Durata Therapeutics International B.V.

DALBAVANCIN FOR INJECTION

for Treatment of Acute Bacterial Skin and Skin Structure Infections

NDA 021-883

Briefing Document

Presented to the FDA Anti-Infective Drugs Advisory Committee

31 March 2014

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

1 EXECUTIVE SUMMARY

1.1 Introduction

Dalbavancin is a second-generation semisynthetic lipoglycopeptide antibiotic. In vitro and in vivo nonclinical microbiology and pharmacology and clinical data provide evidence for the potential therapeutic usefulness of dalbavancin in the treatment of clinical infections caused by Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). In addition, dalbavancin has a long terminal elimination half-life ($T_{1/2}$) which provides for a once-weekly dosing regimen (Section 5.2); a complete course of therapy consists of 2 single weekly doses of dalbavancin administered on Day 1 and Day 8.

This Advisory Committee Briefing Document describes the development program leading to clinical evidence of the efficacy and safety of dalbavancin in the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by Gram-positive bacteria, including those infections caused by MRSA.

1.2 Proposed Indication

Dalbavancin for Injection is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) as caused by susceptible strains of the following Gram-positive microorganisms:

- *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains)
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*)

1.3 Development and Regulatory History

1.3.1 Corporate Sponsorship of Dalbavancin

Dalbavancin has undergone sponsorship and clinical development by 4 separate corporate entities since it was originally discovered by Marion Merrell Dow, and later developed for clinical testing by Biosearch Italia (first-in-human study in United Kingdom, 1999). Biosearch Italia subsequently partnered with Versicor Pharmaceuticals Inc., who submitted the IND to begin US trials (2000). The 2 companies later merged forming Vicuron Pharmaceuticals, Inc. (2003), and this combined company conducted the majority of the early phase 1 and phase 2/3 trials. Vicuron originally submitted NDA 021-883 in December 2004, seeking approval for complicated skin and skin structure infections (cSSSI), prior to Vicuron's acquisition by Pfizer Inc. (September 2005).

Pfizer divested of Vicuron Pharmaceuticals in December 2009, and Vicuron and dalbavancin were acquired by Durata Therapeutics, Inc.

1.3.2 United States Regulatory History

The clinical development of dalbavancin was performed in concordance with standard approaches as used for the evaluation of newer antibacterial agents and guidances for Good Clinical Practice.

During the initial review cycle for the original NDA (submitted by Vicuron), the clinical basis for support for the efficacy and safety of dalbavancin for treatment of complicated skin and skin structure infections (cSSSI) were pivotal trial VER001-9 and a supportive trial VER001-8 for the treatment of uncomplicated skin and skin structure infections (uSSSI). Both of these trials were conducted in the 2003-2004 timeframe.

Shortly after the acquisition of Vicuron and dalbavancin by Pfizer, NDA 021-883 received the 1st of 3 Approvable action letters from the FDA (September 2005, June 2006 and December 2007). The 1st and 2nd Approvable actions did not contain any clinical issues. The pivotal study VER001-9 was considered adequate and well-controlled and served as the basis of a positive benefit risk assessment, supported by the safety and efficacy data available in the other clinical trials. Instead, the first 2 Approvable action letters focused on manufacturing questions, while the 3rd letter addressed the Agency's emerging thinking about the importance of the noninferiority margin in clinical trial design, and in particular, its justification in the supportive uSSSI trial, VER001-8. Pfizer provided complete responses to all 3 Approvable letters, but later withdrew the Application (September 2008) for reasons unrelated to safety or efficacy.

Durata initiated End-of-phase 2 dialog with the Division of Anti-Infective Products (DAIP) in June 2010 regarding the clinical and nonclinical data needed to support registration of dalbavancin for the newly-defined indication of ABSSSI, based upon the draft Guidance for ABSSSI (August 2010; Appendix 1), which contained recommendations for establishment of the primary efficacy endpoint, based on early assessments of efficacy (48-72 hours after the start of therapy), related to absence of fever and cessation of spread of the lesion. It was expected that the cSSSI study VER001-9 would constitute the 1st adequate and well-controlled trial, and that a second, Guidance-compliant trial (DUR001-301) would be the 2nd pivotal trial to support registration. Durata subsequently chose to perform a second new trial, of identical design to DUR001-301, believing it would enhance the clinical package now targeting the new early clinical endpoint. The Division agreed with this decision. Both trial protocols were the subject of a Special Protocol Assessment agreement (SPA) with the Agency in 2010-2011. Both began accruing patients worldwide in early-to-mid 2011, and completed enrollment by December 2012.

In October 2012, dalbavancin received a designation of Qualified Infectious Disease Product (QIDP) under the Generating Antibiotic Incentives Now (GAIN) Act, Title VIII of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), as having met the requirements of an agent to treat a serious or life-threatening condition caused by a "qualifying pathogen," as defined in the statute, namely methicillin-resistant *Staphylococcus aureus* (MRSA).

Following pre-NDA meetings in June-July 2013, in which Durata provided preliminary evidence from the 2 pivotal trials of having met the efficacy criteria defined in the 2010 draft Guidance, the company submitted its updated version of NDA 021-883 on September 26, 2013. DAIP issued the final ABSSSI Guidance in October 2013 – 1 month after the submission of the Application by Durata (Appendix 2). The final Guidance, which contained a newly-defined primary endpoint of clinical response at 48-72 hours which is based solely on decrease in lesion area from Baseline. Both DUR001-301 and 302 had prospectively-defined such sensitivity analyses as alternative primary endpoints in advance of the issue of the final Guidance.

NDA 021-883 was accepted for review by the Agency on November 25, 2013, and was assigned a Priority Review classification, with a Prescription Drug User Fee Act (PDUFA) action date of May 26, 2014.

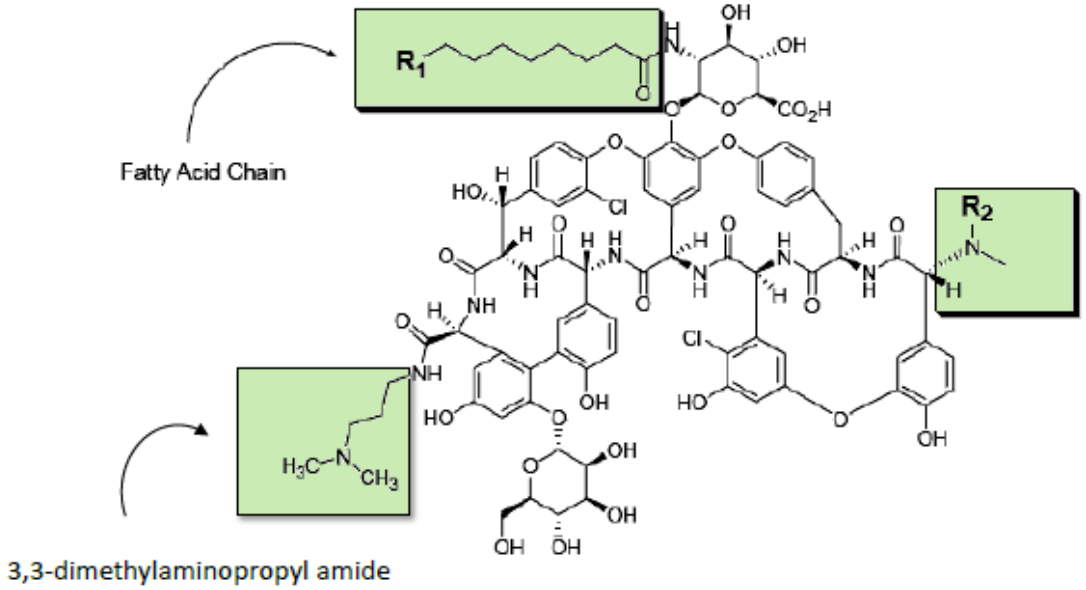
While Study VER001-9 contributes significantly to both the safety and efficacy conclusions in the NDA, this briefing document will focus on a detailed presentation of data from the two ABSSSI studies, DUR001-301 and DUR001-302.

1.4 Chemistry and Pharmaceutical Summary

Dalbavancin for injection is a bactericidal lipoglycopeptide synthesized from a fermentation product of *Nonomuraeae* sp., A-40,926.

Dalbavancin, a hydrochloride salt, is a mixture of five closely-related, biologically-active homologs (A_0, A_1, B_0, B_1, and B_2, Figure 1), which is a common outcome of antibacterial core molecules produced by microbiological fermentation. The component B_0 is the major component of dalbavancin (≥80%).

Figure 1. Structure of Dalbavancin



The homologs share the same core structure and differ in the fatty acid side chain of the N-acylaminoglucuronic acid moiety structure (which extends the half-life of the compound), and/or the presence of an additional methyl group on the terminal amino group.
The 3,3-dimethylaminopropylamide substituent, which is common to all dalbavancin components, enhances the antibacterial activity of the molecule. All 5 homologs have similar antibacterial activity (Section 1.5.1). For the detailed description of the structures of dalbavancin homologs, see Section 3.1.

1.5 Nonclinical Summary

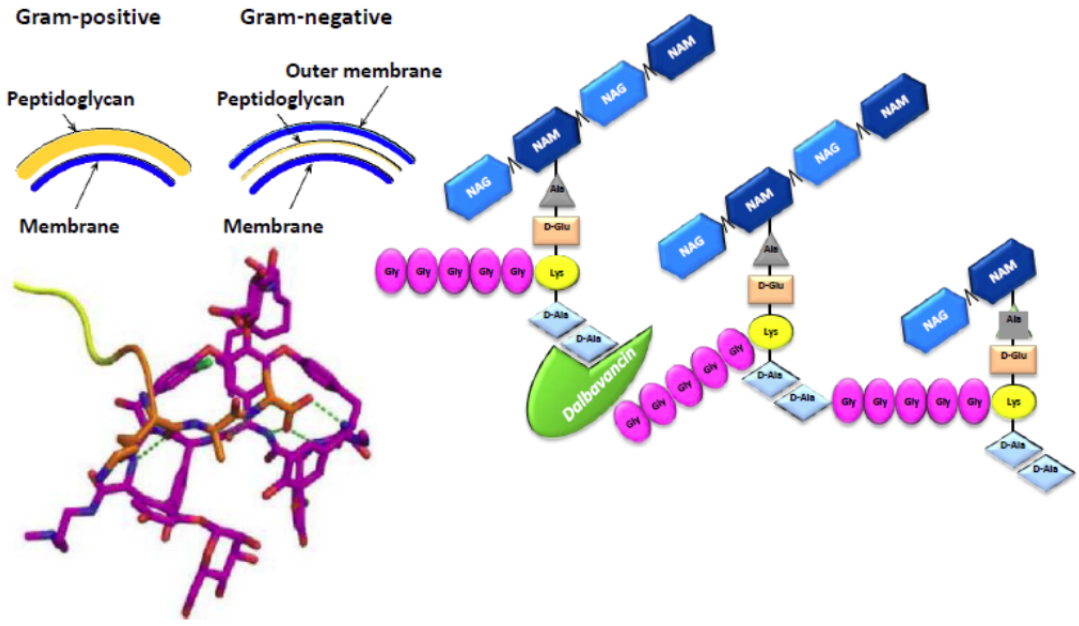
1.5.1 Primary Pharmacodynamics Studies

The dalbavancin primary pharmacodynamics program focused on microbiological activity, and included studies of the mechanism of action of dalbavancin, its antibacterial spectrum and potency in vitro, its activity in vivo in animal infection models, and its potential for development of resistance. Proposed susceptibility interpretive criteria were determined for the establishment of dalbavancin breakpoints.

1.5.1.1 Mechanism of Action

Dalbavancin's mechanism of action is similar to that of other members of the glycopeptide class of antibiotics - interfering with the transpeptidation and transglycosylation step in cell wall synthesis mediated by binding to the D-ala-D-ala terminus of the stem pentapeptide present in nascent peptidoglycan, which is prominent in Gram-positive bacteria (Figure 2). Binding to this substrate inhibits the cross-linking reactions that strengthen the bacterial cell wall.

Figure 2. Dalbavancin Mechanism of Action



1.5.2 In vitro Activity

Dalbavancin is bactericidal in vitro and in vivo to most staphylococcal species, including MRSA and VISA isolates, as well as most streptococcal species. Dalbavancin is more consistently bactericidal than vancomycin and teicoplanin, a glycopeptide antibacterial approved outside the United States. Important pharmacokinetic/pharmacodynamic (PK/PD) parameters with regard to the bactericidal effect include area under the plasma-concentration curve over minimal inhibitory concentration (AUC/MIC), and to a lesser degree, time above MIC (T>MIC). Minimum bactericidal concentrations (MBCs), or concentrations producing at least a 3 $\log_{10}$ reduction in titer in time-kill experiments, are below unbound dalbavancin levels maintained in human plasma throughout the dosing interval with the proposed 2-dose regimen. The MIC values of all of the homologs against a set of staphylococcal, streptococcal and enterococcal strains were similar to those of B_0 (within one dilution). Two metabolites, hydroxydalbavancin (OH-dalbavancin) and mannosylaglycone metabolite (MAG), a metabolite and related chemical processing impurity and degradation product, have lower in vitro activity than the 5 major dalbavancin homologs (Section 4.2.3).

1.5.3 Microbiological Data from Worldwide Surveillance Studies

Clinical isolates of staphylococci and streptococci tested in surveillance and other studies included MRSA and multiple drug-resistant (MDR) strains.

Prospective worldwide surveillance of the in vitro potency of dalbavancin, in comparison with other antimicrobial agents, was begun in 2002 and continued through 2012 as of the time of the preparation of this Application. More than 150,000 Gram-positive isolates were collected, mainly (>125,000) from patients in the United States and Europe. Over 70,000 of the isolates were from 2007 through 2012. The emphasis, particularly in recent years, has been on the species that are most relevant to ABSSSI. Overall, more than 60,000 of the surveillance isolates were *S. aureus*, and more than 7,000 were β-hemolytic streptococci. The MIC_{90} was 0.06 µg/mL for *S.aureus,* 0.12 µg/mL for coagulase negative staphylococci, ≤ 0.03 µg/mL for beta-hemolytic streptococci, 0.06 for viridans group streptococci and ≤ 0.03 for *S.pneumoniae*.

The data for *S. aureus* are described in Table 1. By both CLSI and EUCAST criteria, 52.5% of the *S. aureus* isolates were methicillin-resistant, based on oxacillin MIC data. By CLSI criteria, there were no glycopeptide-resistant or glycopeptide-intermediate *S. aureus* isolates, whereas by EUCAST criteria, there were a small number of isolates with intermediate susceptibility to vancomycin (VISA; < 0.1%). The highest dalbavancin MIC was 0.5 µg/mL (< 0.1% of isolates; Table 47).

Table 1 Comparative Activity of Dalbavancin Against 39,824 Isolates of *S. aureus* from the US (2002-2012)

Antimicrobial Agent	MIC (µg/mL)			%S /%I / %R[a]	
	50%	90%	Range	CLSI	EUCAST
Dalbavancin	0.06	0.06	≤0.03 – 0.5	- / - / -	- / - / -
Vancomycin	1	1	≤0.12 – 4	>99.9 / <0.1 / 0.0	>99.9 / 0.0 / <0.1
Oxacillin	>2	>2	≤0.25 – >2	47.5 / 0.0 / 52.5	47.5 / 0.0 / 52.5
Erythromycin	>2	>2	≤0.25 – >2	35.9 / 0.9 / 63.2	36.1 / 0.4 / 63.5
Clindamycin	≤0.25	>2	≤0.25 – >2	76.5 / 0.2 / 23.3	76.1 / 0.4 / 23.5
Daptomycin	0.25	0.5	≤0.12 – 4	99.9 / - / -	99.9 / 0.0 / 0.1
Levofloxacin	≤0.5	>4	≤0.5 – >4	56.6 / 1.1 / 42.3	56.6 / 1.1 / 42.3
Linezolid	1	2	≤0.25 – >8	>99.9 / 0.0 / <0.1	>99.9 / 0.0 / <0.1
Tetracycline	≤4	≤4	≤4 – >8	95.1 / 0.5 / 4.4	89.7 / 0.4 / 9.9

[a] Criteria as published by CLSI 2013 and EUCAST (2013)
[b] Data from R. Jones, JMI Laboratories, SENTRY database.

In general, dalbavancin had greater in vitro potency than other glycopeptides and most other classes of comparators tested. Strains resistant to other classes of antimicrobials currently used to treat Gram-positive infections were susceptible to dalbavancin. As judged by $MIC_{50/90}$s and MIC ranges, the potency of dalbavancin for *S. aureus* was greater than those of all of the comparators, which included erythromycin, clindamycin, daptomycin, levofloxacin, linezolid, trimethoprim/sulfamethoxazole (TMP/SMX) and tetracycline.

For detailed results from surveillance studies relevant to ABSSSI pathogens, see Section 7.2.1.

1.5.4 Animal Models of Infection

In vivo models of systemic and localized Gram-positive bacterial infection utilized immunocompetent and immunocompromised rodent and immunocompetent rabbit, such as endocarditis, granuloma pouch and lobar pneumonia. Staphylococcal strains used to infect the animals included susceptible, resistant, or strains with reduced susceptibility to some currently marketed antibiotics, such as methicillin-susceptible *Staphylococcus aureus* (MSSA), MRSA and vancomycin-intermediate *S. aureus* (VISA). Endpoints included survival and bacterial burden in different tissues. Consistent with its in vitro antibacterial potency and pharmacokinetics (PK), in all of these studies dalbavancin was active at lower and/or less frequent doses than the antimicrobial agents used as comparators.

Efficacy against *S. aureus* was correlated with drug exposure in experiments in rats, rabbits and immunocompromised mice with infections simulating skin and skin structure infections (SSSI).

1.5.5 Potential for Development of Resistance

Dalbavancin has a low potential for resistance development. Several serial passage experiments were performed in several different laboratories in an attempt to observe gradual

development of resistance to dalbavancin. In one such experiment, *S. aureus* ATCC 25923 and a clinical isolate of *S. haemolyticus* were passaged in Tryptic Soy broth. After 24 passages at sub-MIC concentrations, the maximum MIC of dalbavancin identified during any passage for *S. aureus* ATCC 25923 increased 2-fold (0.25 µg/mL to 0.5 µg/mL), while those of vancomycin and teicoplanin increased 4- and 8-fold, respectively. When the *S. haemolyticus* strain was passaged, the maximal dalbavancin MIC identified at any passage increased 4-fold (from 0.12 to 0.5 µg/mL), the vancomycin MIC 4-fold and the teicoplanin MIC 32-fold.

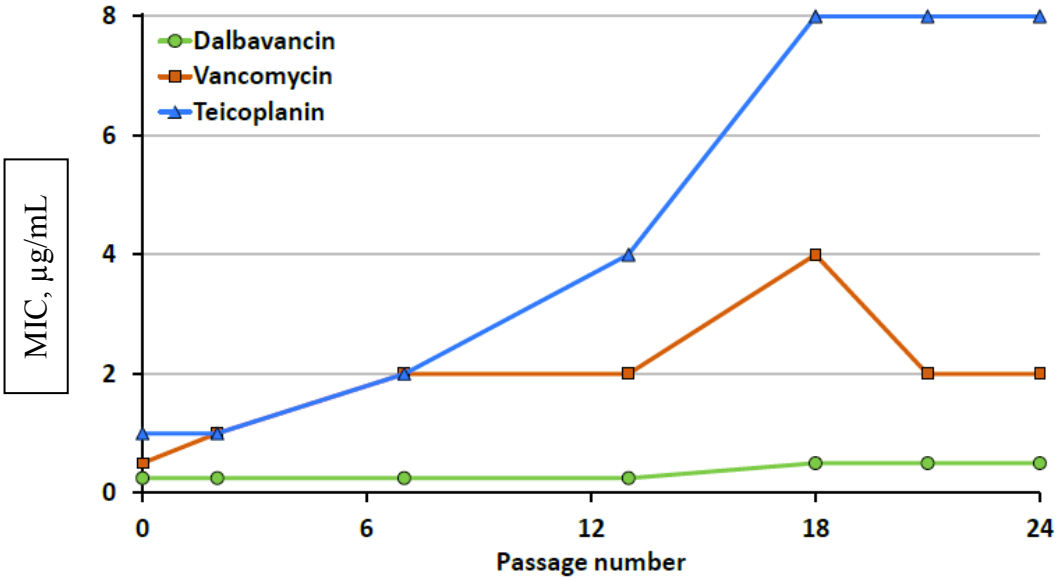
Table 2 shows the MIC values obtained at baseline and after 7, 13 and 24 passages. The time course of resistance emergence is shown in Figure 3.

Table 2. MICs of Dalbavancin, Vancomycin and Teicoplanin for *S. aureus* and *S. haemolyticus* after Serial Passage

Strain	Passage Number	MIC (µg/mL)		
		Dalbavancin	Vancomycin	Teicoplanin
S. aureus ATCC 25923	P0	0.25	0.5	1
	P7	0.25	1	2
	P13	0.25	2	4
	P24	0.5	2	8
S. haemolyticus 4036	P0	0.12	0.5	0.5
	P7	0.12	1	2
	P13	0.12	2	8
	P24	0.5	1	16

Source: Data on file, Lopez 2005.

Figure 3. Serial Passage of *S. aureus* in Dalbavancin, Vancomycin and Teicoplanin.



Source: Data on File, Lopez 2005.

1.5.6 Secondary Pharmacodynamics Studies

Because dalbavancin's mechanism of action is bacteria-specific, it is not expected to interfere with other physiologic processes.

Dalbavancin was evaluated in secondary pharmacodynamics studies in vitro to assess its potential effect on the cardiovascular system (ie, hERG, Purkinje fibers), coagulation (platelet aggregation), and a series of 120 enzymes, receptors, ion channels and uptake sites. In these studies, dalbavancin showed little or no potential for interference with these systems observed at therapeutic concentrations. The low potential for interaction of dalbavancin with other physiologic targets was further supported by an acceptable safety profile in nonclinical safety pharmacology and toxicology studies (Sections 4.1.3 and 4.3) and in human trials (Section 8).

In vitro and in vivo metabolism studies in animals and humans demonstrated that dalbavancin does not interfere with cytochrome P450 (CYP450) activity, and as such, has demonstrated little potential for drug-drug interactions, a finding that was supported by results in Phase 2/3 clinical studies, where no pattern of drug-drug interaction was identified.

1.5.7 Nonclinical Pharmacokinetics, Distribution, Metabolism and Excretion Studies

The PK of dalbavancin were studied in mice, rats, rabbits, dogs, and minipigs, and included tissue distribution and mass balance (excretion) following intravenous (IV) infusion of dalbavancin in single-dose rat and dog studies using radiolabeled drug. An IV minipig study was conducted to examine distribution of dalbavancin to skin. Serum or plasma and exudate PK in mice, rats, and rabbits were determined as part of in vivo infection studies. The

plasma PK profile of dalbavancin was assessed as part of subchronic (28-day and 90-day) rat and dog toxicology studies, as well as a 56-day toxicology study in juvenile rats. In a rat reproductive toxicology study, concentrations of dalbavancin were determined in maternal plasma, maternal milk, and fetal plasma. In vitro studies of the plasma protein binding of dalbavancin were conducted using rat, dog, and human plasma; protein binding ranged from 95% in animals to 93% in humans. Metabolism studies examined the effect on CYP450 activity. Dalbavancin metabolites were qualitatively and quantitatively examined in plasma and excreta of rats, dogs, and humans and were determined to have similar profiles across all species tested.

The proposed clinical dosage regimen consists of 2 IV doses of dalbavancin: a 1000 mg dose on Day 1, followed by a 500 mg dose on Day 8. This regimen provides a peak plasma concentration (C_{max}) of ~ 250 µg/mL and a systemic exposure of ~ 26,000 µg•h/mL (cumulative AUC over 14 days, Sections 1.6 and 5.2.1). Plasma concentrations and exposures of daily dalbavancin that were achieved in repeat-dose toxicology studies in dogs and rats up to 90 days in duration, substantially exceeded the range of C_{max} and AUC expected in clinical use, being 2- to 6.5-fold longer in duration than the proposed clinical exposure period, and approximately 2- to 4-fold higher than clinical plasma exposures (AUC). Exposures observed in reproductive studies in rats and dogs were similar to those obtained in the human therapeutic dose range.

The similarity of the absorption, distribution, metabolism, excretion (ADME) characteristics of dalbavancin across species supported the use of rats and dogs for safety assessment.

1.5.8 Safety Pharmacology and Toxicology Studies

Safety pharmacology studies were conducted to determine the effects of dalbavancin on the central and autonomic nervous systems, the cardiovascular system, the respiratory system, and coagulation components. In studies conducted in mice, rats, dogs, and in tissues from rabbits, no adverse events were noted at exposure levels in adult or juvenile animals that are approximately 2- to 4-fold those in humans at the clinical dose on an exposure (AUC) basis. No effects on mating, fertility and embryo fetal development were observed at exposures similar to the proposed dose.

The preclinical findings in general toxicology studies in adult and juvenile rats and dogs consisted of 4 general responses: transient infusion reactions (observed only in dogs); local skin and vascular toxicity at the injection site (observed in rats and dogs); cytoplasmic vacuoles and/or pigment in multiple tissues, and renal and hepatic target organ toxicity in rats and dogs.

Dogs given IV dalbavancin experienced transient infusion-related reactions at doses ≥ 30 mg/kg/day when infused over 11 to 30 minutes, and generally increased in incidence with dose above this threshold, or when infused at higher concentrations, or faster rates over shorter infusion times. Reactions were characterized by modest hemodynamic changes (decreases in blood pressure and increases in heart rate), ear skin and scleral vessel congestion, muzzle, and/or paw swelling, mucosal pallor, salivation, vomiting, and sedation. Infusion reactions in dogs were attributed to histamine release and may reflect a combination

of the size of the administered dose and/or dose solution concentration and the rate of infusion. These effects were reversed with subsequent administration of noradrenaline. Similar changes were not observed in rats.

Repeated IV administration of dalbavancin was associated with development of dose-related injection site toxicity characterized as microscopic perivascular inflammation and fibrosis and vascular degeneration/thrombosis. A local tolerance study in rabbits confirmed that dalbavancin was more irritating when injected perivenously than intravenously.

The observation of adverse renal effects was consistent with a primary tubular effect resulting in altered tubular function in dogs dosed at 40 mg/kg/day for 28 days (approximately 13 times the human exposure). At high doses, increases in serum urea and/or creatinine were observed. Associated renal structural effects included increased relative renal weight, macroscopic renal pallor, and microscopic tubular changes (dilatation, degeneration, necrosis and basophilia). Nephrotoxicity in rats and dogs is considered related to high tissue exposure. Similar nephrotoxicity has been reported for other members of the glycopeptide class of antibiotics.

The effect on the liver was characterized predominantly by clinical chemistry changes (increased aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP] and gamma-glutamyl transferase [GGT]) in the 90-day dog study, which were observed earlier than histologic or other changes and persisted after histologic findings had reversed. Clinical chemistry changes, primarily increases in AST and ALT activity, were the principal hepatic-associated findings in rats. Studies in dogs demonstrated higher hepatic concentrations of dalbavancin, and hepatocellular necrosis was observed after 2 or more months of dosing at ≥10 mg/kg/day, affording overall exposures that substantially (> 10-fold) exceeded those projected from the proposed human dose regimen. Dalbavancin-related hepatic effects in animals were reversible following cessation of dosing. The mechanism of hepatic toxicity is hypothesized from the fact that dalbavancin and its metabolites, as cationic amphiphilic molecules, bind to the phospholipid components of the hepatocellular membranes (Hallifax 2006).

Dose-dependent and duration-dependent changes in bone marrow function, primarily small reductions in hemoglobin (Hgb), hematocrit (HCT) and erythrocytes (RBCs), and variations in platelets were observed in rats and dogs. These findings were observed at doses with plasma exposures at least 6-fold above the clinical exposure and/or with dosing durations at least 2-fold longer than the clinical exposure at the proposed dosage regimen for ABSSSI. Effects were generally of low magnitude (5% to 30% below concurrent controls) and were reversible with cessation of dosing.

Dalbavancin crosses the placenta and is excreted into milk in rats. Reproductive toxicity studies in rats and rabbits at maternally toxic doses showed no evidence of a teratogenic effect. In rats, the paternal and maternal NOELs, as well as NOELs for mating and fertility and embryo-fetal development afforded exposures that were similar to those expected in humans receiving the proposed therapeutic regimen.

Dalbavancin did not demonstrate any effects on glucose homeostasis in test animal species. No results suggesting effects on immunotoxicity were observed. Dalbavancin was not shown to be genotoxic in vitro or in vivo. Carcinogenicity studies were not conducted due to the expected short duration of administration and the absence of a genotoxic or pre-neoplastic signal.

1.5.9 Nonclinical Safety Conclusion

The nonclinical safety evaluation program supports the proposed clinical use of dalbavancin for the treatment for ABSSSI.

1.6 Clinical Pharmacology Summary

The PK of IV dalbavancin were studied in subjects given single-dose regimens ranging from 70 mg to 1500 mg, and multiple-dose regimens ranging from a total 1-week dose of 480 mg to 1600 mg administered over 7 days, and once-weekly doses up to a total of 4500 mg given over 8 weeks. Plasma concentrations were determined in healthy volunteers, special populations (including those with renal and hepatic impairment, and in adolescent children), and patients using population PK. Dalbavancin PK exhibited low inter-individual variability, were predictable and consistent with dose proportionality, and found to be similar between patients and healthy subjects. Dalbavancin is eliminated by both renal and non-renal pathways. Dosage adjustment is not required for mild to moderate renal impairment, or for subjects with severe renal impairment receiving regularly-scheduled dialysis. Based on the PK parameters and simulations, a dosage adjustment (25% dose reduction) is recommended for patients with severe renal impairment who do not receive regular dialysis.

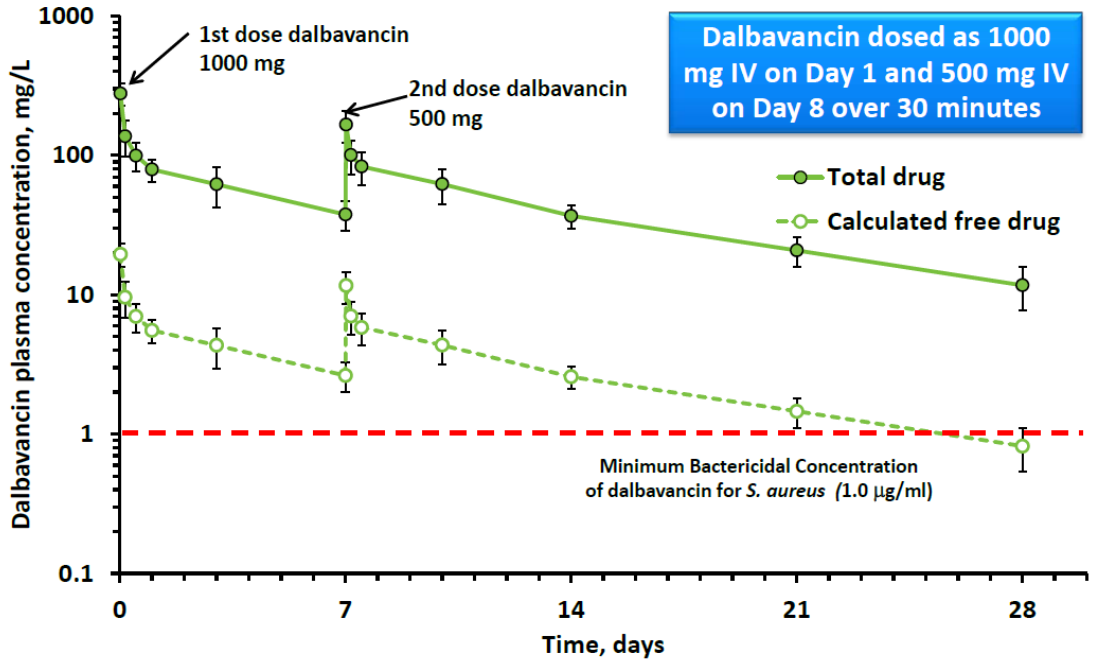
Dalbavancin has a β half-life ($t_{1/2}$) of > 8 days (~200 h) and a terminal half-life ($T_{1/2}$) of > 14 days (~346 h), allowing for clinical safety and efficacy assessment using a once-weekly dosing regimen of 1000 mg on Day 1 and 500 mg on Day 8 - the proposed therapeutic dosage regimen for the treatment of ABSSSI in adult patients, such that serum concentrations above the MBC for typical Gram-positive ABSSSI pathogens are sustained throughout the 2-week dosing interval.

1.6.1 Basic Pharmacokinetic Properties of Dalbavancin

A detailed description of dalbavancin PK is covered in Table 19 in Section 5.2.1. Following administration of single doses of dalbavancin up to 1000 mg, drug exposure, as measured by AUC, increased in a dose-proportional manner. Mean C_{max} and $AUC_{0\text{-}336H}$ for a single 1000 mg dose were 287 mg/L and 23,443 mg•h/L, respectively. Almost 50% and 70% of the exposure is observed through the first and second weeks postdose, respectively. Approximately 90% of drug exposure is observed through 5 weeks postdose. The predominant β $t_{1/2}$ was approximately 8.5 days (204 h) while the terminal phase $T_{1/2}$ was approximately 2 weeks (346 h). Estimates of dalbavancin total clearance (CL) were consistent across studies and did not vary with dose. Mean CL was estimated as 0.0513 L/h. The variability of the PK parameters, both across and within studies and dose cohorts, was low.

In the multiple-dose studies, dalbavancin CL was consistent and approximately 0.05 L/h across all dosage cohorts; no relationship was observed between PK and gender. The proposed clinical dosage regimen of 1000 mg on Day 1 and 500 mg on Day 8 is recommended for patients with adequate renal function or for those who are receiving regularly-scheduled dialysis, and is consistent with a PK rationale for providing sustained concentrations above the MBC for most Gram-positive pathogens using the proposed weekly 2-dose regimen (Figure 4).

Figure 4. Dosing Rationale: Once-Weekly Dosing Regimen of Dalbavancin



Abbreviation: MBC = minimum bactericidal concentration

This regimen demonstrated no accumulation when dosing was extended to weekly dosing with additional 500 mg doses for up to a total of 8 weeks (Study DUR001-104). A weekly multiple dosing regimen does not substantially affect the PK profile of dalbavancin when extended over 4, 6 or 8 weeks of dosing.

1.6.2 Comparison of Pharmacokinetics of Dalbavancin to Marketed Glycopeptide Antibacterials

The PK of dalbavancin are distinctive compared with the 2 US-marketed glycopeptides: vancomycin and telavancin. Dalbavancin has a $T_{1/2}$ of > 14 days, allowing for weekly drug administration. Conversely, the $T_{1/2}$ for the 2 marketed glycopeptide products are only a few to several hours and require daily dosing, and in the case of vancomycin, 2 or 3 doses per day.

Vancomycin has a terminal $T_{1/2}$ of 4 to 6 hours and a mean plasma CL of 0.058 L/h/kg (vancomycin prescribing information). The majority of administered drug is excreted in the urine with a mean renal CL of 0.048 L/h/kg. The drug is approximately 55% serum protein

bound. The shorter vancomycin $T_{1/2}$ requires the drug to be administered at least twice daily in order to maintain therapeutic concentrations. However, for patients with impaired renal function, the terminal elimination $T_{1/2}$ is significantly prolonged and the total body CL is reduced (Evans 1992). The prolonged $T_{1/2}$ observed for vancomycin in subjects with a CL_{Cr} of <10 mL/min is approximately 6 days (Matzke 1984) and similar to the predominant $t_{1/2}$ observed for dalbavancin. Vancomycin PK are influenced by renal impairment and other diseases, and are markedly changed in geriatric patients and in burn patients (Evans 1992, Matzke 1984, Cutler 1984, Rybak 1990). These factors influence the interpatient variability observed for vancomycin, which is larger than that described for dalbavancin. Vancomycin's larger inter-patient variability and narrow therapeutic window require drug monitoring and subsequent dosage adjustment throughout therapy (Evans 1992).

Telavancin PK are similar to those of vancomycin and distinctly different from those of dalbavancin (Vibativ® Prescribing Information). Telavancin has a relatively short terminal $T_{1/2}$ (approximately 8 hours). Similar to vancomycin, the effect of renal impairment is more pronounced than that observed for dalbavancin. In a phase 1 renal impairment study, the mean $AUC_{0\text{-inf}}$ values were approximately 13%, 29%, and 118% higher for subjects with CL_{Cr} > 50 to 80 mL/min, > 30 to 50 mL/min, and ≤ 30 mL/min, respectively. Due to the reduced clearance of telavancin in patients with renal impairment, a dosage adjustment is recommended in patients with a CL_{Cr} ≤ 50 mL/min.

Dalbavancin is not extensively metabolized, although 2 minor metabolites are found in human urine but not in plasma, with 1 of these, OH-dalbavancin, measured in urine to the extent of 8 to 12% (Section 5.2.1.3). Vancomycin and telavancin are also not extensively metabolized. After administration of telavancin, 3 metabolites were observed in a mass balance study; these metabolites accounted for <10% of the radioactivity in urine and <2% of the radioactivity in plasma (Vibativ® Prescribing Information).

1.7 Clinical Efficacy Summary

1.7.1 Phase 3 Clinical Trials Relevant to the Claimed Indication

The clinical program to evaluate the efficacy of IV dalbavancin for the treatment of ABSSSIs or cSSSIs caused by Gram-positive bacteria comprised 3 phase 3 studies: the 2 recently-conducted pivotal ABSSSI trials (DUR001-301, and DUR001-302) and the cSSSI trial from the original Application (VER001-9), as supportive in this Application. A detailed description of the efficacy results from these individual trials, as well as an integrated analysis of the results across the 3 studies, are described in (Section 6).

All 3 studies were conducted in clinical centers worldwide according to national and international guidelines for Good Clinical Practice.

1.7.1.1 Trial Design

PROTOCOLS DUR001-301 AND DUR001-302 (ABSSSI, 2011 TO 2012)

Protocols DUR001-301 (Section 6.6.1) and DUR001-302 (Section 6.6.2) were of identical design, based on the 2010 Draft FDA Guidance for treatment of ABSSSI (Appendix 1). The

2 randomized, multicenter, double-blind, double dummy studies compared IV dalbavancin (1000 mg on Day 1 and 500 mg on Day 8) to IV vancomycin for at least 3 days, with a possible switch to oral linezolid after 3-4 days of IV therapy, to complete a total duration of 10-14 days of therapy in patients demonstrating clinical improvement. Oral and IV placebo medication was utilized in order to maintain the blinded trial design, and dedicated unblinded onsite pharmacy personnel were the only people at the investigators' locations who maintained direct involvement with the preparation of the study drug and its documentation. Dosage adjustment options based on renal function were recommended in the clinical protocols for either treatment assignment.

Patients with either cellulitis, major abscess or a traumatic wound infection were enrolled in the 2 studies; enrollment of patients with a major abscess was capped at 30%. Presenting lesion size requirements were ≥ 50 cm^2 on the face or ≥ 75 cm^2 elsewhere on the body. Most patients presented with a lesion substantially larger than the minimum required dimensions. Patients were to also have had at least 1 systemic sign of infection [(temperature ≥ 38°C (approximately 84%), WBC > 12,000 cells/mm^3 (approximately 40%) or bands ≥ 10% (approximately 18%)].

PROTOCOL VER001-9 (CSSSI, PRIOR TO 2004)

Protocol VER001-9, which compared dalbavancin to linezolid, was conducted according to regulatory guidance in place at the time (US Depatment of Health and Human Services, Food and Drug Administration 1998), in which complicated skin and skin structure infection (cSSSI) was the target indication, with a primary efficacy endpoint of clinical response at Test of Cure (Day 28, or approximately 14 days after completion of therapy) in the CE population. Dalbavancin dosing was the same as in the ABSSSI trials referenced above. Details of the outcome of this trial are described in Section 6.6.3.1.

1.7.1.2 Patient Demographics and Baseline Characteristics: Protocols DUR001-301 and DUR001-302

Demographic and Baseline characteristics were similar between dalbavancin and comparator groups in the 2 phase 3 ABSSSI clinical trials (Table 3). All treatment groups included similar proportions of male and female patients, and the majority of patients were White. The mean ages between dalbavancin and comparator groups were similar (DUR001-301: 48.8 versus 48.9 years; DUR001-302: 49.1 versus 51.4 years). Geographically, the majority of patients were enrolled in Europe, South Africa and Asia, with 30-40% of patients coming from North America. Most patients (~85% in both groups from each study) presented with fever (≥ 38°C) at Baseline, and other disease characteristics were similar between groups. Median lesion area was similar between groups within and across studies. The most common infection type in both studies was cellulitis.

Table 3. Demographics and Baseline Characteristics, Phase 3 Studies DUR001-301/302 (ITT Populations)

	DUR001-301		DUR001-302	
	Dalbavancin N=288	Vancomycin/ Linezolid N=285	Dalbavancin N=371	Vancomycin/ Linezolid N=368
Age, yr.				
Mean (SD)	48.8 (15.30)	48.9 (15.08)	49.1 (16.54)	51.4 (16.16)
Range (min, max)	18, 84	18, 84	18, 85	18, 84
Male, n(%)	170 (59.0)	173 (60.7)	223 (60.1)	201 (54.6)
Race or Ethnic Group, n(%)				
White	264 (91.7)	259 (90.9)	328 (88.4)	320 (87.0)
Black or African American	16 (5.6)	19 (6.7)	13 (3.5)	17 (4.6)
Asian	1 (0.3)	2 (0.7)	27 (7.3)	30 (8.2)
Other[a]	7 (2.4)	5 (1.8)	3 (0.8)	1 (0.3)
Region of Enrollment				
United States/Canada	123 (42.7)	121 (42.5)	115 (31.0)	114 (31.0)
Europe, S. Aftrica, and Asia	165 (57.3)	164 (57.5)	256 (69.0)	254 (69.0)
Temperature ≥ 38°C (%)	243/284 (85.6)	242/284 (85.2)	306/365 (83.8)	310/365 (84.9)
WBC >12,000 cells/mm^3 (%)	98/259 (37.8)	104/254 (40.9)	149/368 (40.5)	146/367 (39.8)
Bands ≥10% (%)	63/238 (26.5)	66/244 (27.0)	48/241 (19.9)	42/234 (17.9)
Elevated hs-CRP (mg/L) (%)	253/284 (89.1)	258/284 (90.8)	332/366 (90.7)	327/367 (89.1)
SIRS criteria met, (%)	175/284 (61.6)	175/284 (61.6)	157/368 (42.7)	161/368 (43.8)
Diabetes mellitus				
History, (%)	43 (14.9)	30 (10.5)	35 (9.4)	62 (16.8)
Fasting glucose-defined prediabetes/diabetes (%)	39.2	41.4	38.5	37.5
Median area of lesion, cm^2 (range [min,max])	333.00 (25.6, 3400.0)	367.75 (77.6, 3675.0)	313.50 (85.1, 5100.0)	362.40 (72.0, 3922.0)
Pathogen at Baseline (MicroITT population)	153 (53.1)	155 (54.4)	184 (49.6)	174 (47.3)
Infection type, n (%)				
Major abscess	72 (25.0)	86 (30.2)	90 (24.3)	87 (23.6)
Cellulitis	156 (54.2)	147 (51.6)	198 (53.4)	202 (54.9)
Traumatic wound/-surgical site infection	60 (20.8)	52 (18.2)	82 (22.1)	79 (21.5)

[a] Includes patients classified racially/ethnically as American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or Other

Abbreviation: hs-CRP = high sensitivity C-reactive protein

1.7.1.3 Primary Efficacy Endpoint - ABSSSI

Table 4 summarizes overall clinical response rates in the 2 pivotal ABSSSI studies at the pre-specified primary efficacy endpoint, as contained in the FDA SPA agreements. Clinical Responders were defined as patients whose lesion had no increase in area, length, or width

relative to Baseline, and who had a temperature consistently ≤ 37.6°C, upon repeated measurement, within the 48-72 hour period after initiation of therapy.

Table 4 Clinical Response Rates in ABSSSI Studies at 48-72 Hr after Initiation of Therapy (Primary Endpoint, 2010 Draft Guidance)

	DUR001-301		DUR001-302	
	Dalbavancin N=288	Vancomycin/-Linezolid N=285	Dalbavancin N=371	Vancomycin/-Linezolid N=368
Clinical responder	240 (83.3%)	233 (81.8%)	285 (76.8%)	288 (78.3%)
Clinical nonresponder	48 (16.7)	52 (18.2)	86 (23.2)	80 (21.7)
Difference (95% CI)	1.5% (-4.6, 7.9)		-1.5% (-7.4, 4.6)	

In both studies, dalbavancin was found to be non-inferior to vancomycin/linezolid for the primary efficacy endpoint.

ALTERNATIVE PRIMARY ENDPOINT – ABSSSI (SENSITIVITY ANALYSIS – REDUCTION IN LESION SIZE FROM BASELINE)

One month following the submission of this Application, in October 2013, the FDA Guidance for ABSSSI was finalized (Appendix 2), and the new primary endpoint is based on the single variable of percent change in lesion size (area) from Baseline at 48-72 hours after initiation of study drug. A clinical responder was defined as having a reduction in lesion area of ≥ 20% from Baseline, with the patient not having received any rescue antibiotic therapy, and being still alive at the time of the assessment. A prospectively-defined sensitivity analysis on the final Guidance primary endpoint was performed for the 2 ABSSSI studies. The results from the individual studies demonstrated non-inferiority of dalbavancin to a regimen of vancomycin/linezolid, as relevant to the new endpoint (Table 5).

Table 5. Clinical Response Rates in ABSSSI Studies at 48-72 Hours After Initiation of Therapy (Primary Endpoint from 2013 Final Guidance)

≥ 20% Reduction in Lesion Area from Baseline						
	DUR001-301			DUR001-302		
	Dalbavancin n (%)	Comparator n (%)	Difference (95% CI)	Dalbavancin n (%)	Comparator n (%)	Difference (95% CI)
ITT	N=288	N=285		N=371	N=368	
Responder	259 (89.9)	259 (90.9)	-1.0 (-5.7, 4.0)	325 (87.6)	316 (85.9)	1.7 (-3.2, 6.7)
Non-responder	29 (10.1)	26 (9.1)		46 (12.4)	52 (14.1)	

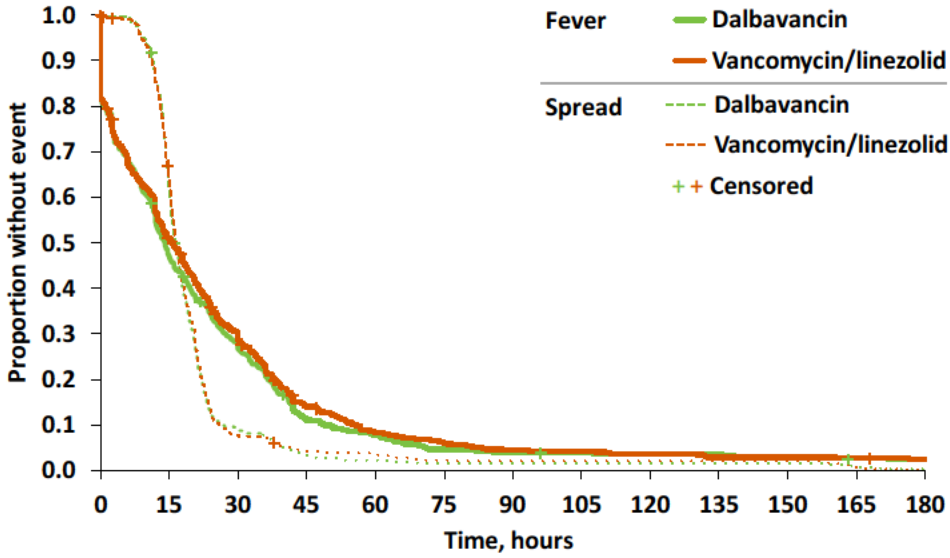
Abbreviation: ITT = intent-to-treat

1.7.1.4 Time to Analyses of Primary Endpoints In Pivotal Studies DUR001-301 and DUR001-302 (pooled)

TIME TO PRIMARY ENDPOINT PER 2010 FDA DRAFT GUIDANCE (POOLED)

Kaplan-Meier plots of pooled analyses for the pivotal phase 3 trials DUR001-301 and DUR001-302 for the primary endpoint of cessation of spread and absence of fever within 48-72 hours from the start of therapy (FDA Draft Guidance, 2010) are shown in Figure 5. Mean time to absence of fever and cessation of spread for each patient's ABSSSI lesion in these studies over the course of treatment was similar between the two treatment groups in pooled data from both studies. Cessation of spread (dashed lines) tended to occur within 24 hours, while almost all patients were afebrile by 72 hours (solid lines).

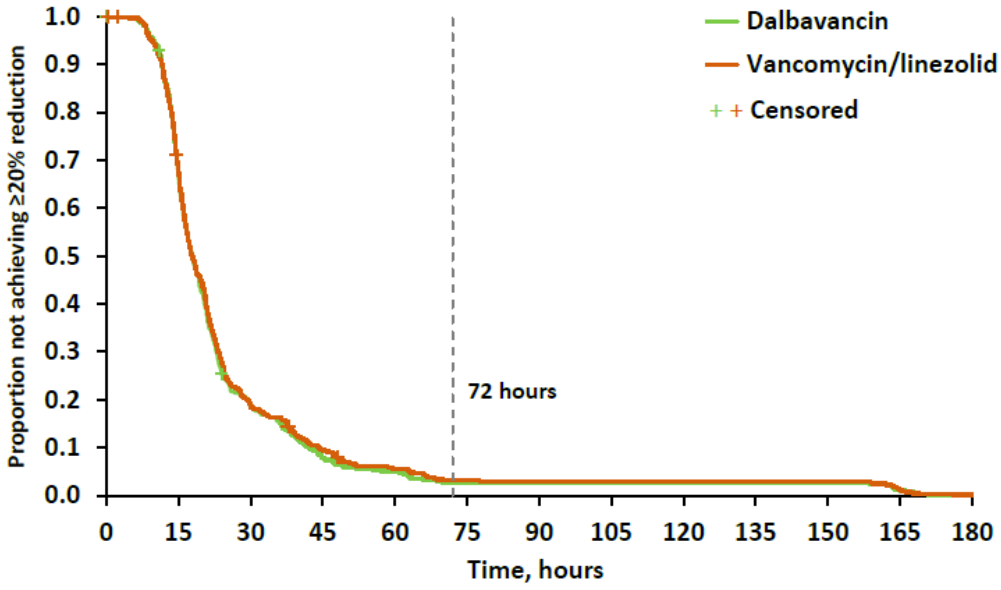
Figure 5. Time to Absence of Fever and Cessation of Spread (Studies DUR001-301/302 pooled)



ALTERNATIVE TIME TO PRIMARY ENDPOINT FROM 2013 FDA FINAL GUIDANCE (POOLED)

A time to event assessment of achievement of $\geq$ 20% reduction in lesion size for the pooled analysis of pivotal phase 3 trials DUR001-301 and DUR001-302 is illustrated by the Kaplan-Meier plots in Figure 6. Most events (> 90%) were observed at evaluation points taken at the first 48 hours from the initiation of treatment, and the remainder were observed by 48-72 hours in a similar manner between treatment groups.

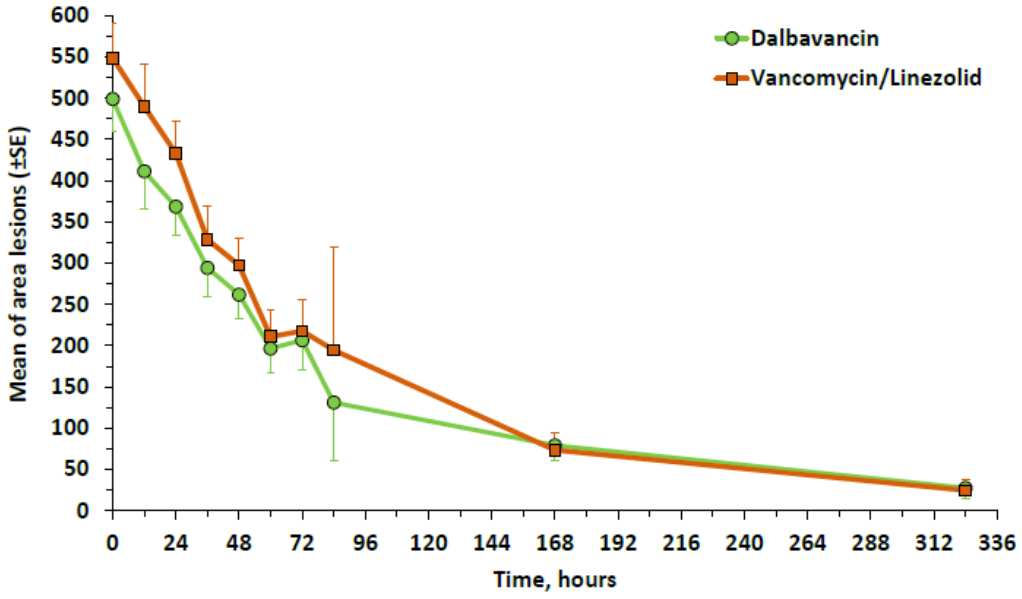
Figure 6. Time to ≥ 20% Reduction in Lesion Size (Studies DUR001-301/302 pooled)



ALTERNATIVE EFFICACY ANALYSIS: REDUCTION IN MEAN LESION AREA OVER TIME

Patients' lesion area decreased over time in both dalbavancin and comparator groups. Figure 7 describes the reduction in mean lesion area over time. In the pooled analysis from both ABSSSI trials, mean lesion area decreased rapidly over the 48-72 hour assessment period and the lesion was essentially absent by the 8th day (192 hours) following initiation of therapy.

Figure 7. Reduction in Mean Area of Skin Lesion Over Time (Studies DUR001-301/302 pooled)



1.7.1.5 Secondary Efficacy Analyses

CLINICAL STATUS AT END OF TREATMENT - ABSSSI

In the ABSSSI studies, prespecified key secondary outcome measures were Clinical Status at end of treatment (Day 14) in the clinically evaluable (CE-EOT) and intent-to-treat (ITT) populations. Clinical status was also determined at the short-term follow-up (SFU) visit (Day 28). Investigator assessments of clinical outcome at the EOT and SFU visits were also determined.

Patients were programmatically defined as a Clinical Status of success if lesion size, as defined by erythema, had decreased from Baseline, the patient was afebrile ($\leq 37.6^{o}$ C), local signs of fluctuance and localized heat/warmth were absent, and other local sysmptoms of the infection were no worse than mild in severity. A patient was programmatically defined as a clinical status of failure if any of the above criteria was not met, or if the patient received a new non-study systemic antibacterial treatment for the ABSSSI at any time from the first dose of study drug through the visit, the patient died during the study period up to the visit, the patient required surgical intervention more than 72 hours after the start of therapy for treatment of the ABSSSI under study, unless preplanned as part of non-drug therapy for the ABSSSI, or the patient received study therapy for the ABSSSI under study beyond the protocol treatment period as a result of the investigator's assessment that additional drug therapy was needed for treatment of the underlying skin infection. Investigator assessment of clinical success was defined as resolution or improvement of all signs and symptoms of the infection to such an extent that no further antibacterial treatment was given. Investigator assessment of clinical failure was defined as any of the following: (1) persistence of $\geqslant 1$ local or systemic signs and symptoms of ABSSSI such that new systemic antibacterial

treatment was given; (2) unplanned surgical intervention > 72 hours after start of therapy for the treatment of ABSSSI (3) TEAE leading to discontinuation of study drug, and patient required additional antibiotic therapy to treat the ABSSSI; (4) received study therapy beyond the protocol treatment period as a result of the investigator's assessment that additional drug therapy is needed for treatment of the underlying skin infection; (5) death during the study period.

Table 6 summarizes the results from these key secondary analyses at EOT. Overall, within each study, the outcomes were similar between treatment groups, as they were at the SFU visit (Table 39).

Table 6. Clinical Status at the EOT Visit (Day 14) in the CE-EOT and ITT Populations

	DUR001-301		DUR001-302	
	Dalbavancin	Comparator	Dalbavancin	Comparator
	n (%)	n (%)	n (%)	n (%)
CE-EOT Population, N1	**N=246**	**N=243**	**N=324**	**N=302**
Clinical Status				
Success	214 (87.0)	222 (91.4)	303 (93.5)	280 (92.7)
Failure	32 (13.0)	21 (8.6)	21 (6.5)	22 (7.3)
Investigator Assessment of Clinical Response at EOT				
Success	233 (94.7)	237 (97.5)	314 (96.9)	290 (96.0)
Failure	12 (4.9)	4 (1.6)	10 (3.1)	12 (4.0)
Indeterminate (due to missing data) [a]	1 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)
ITT Population, N2	**N=288**	**N=285**	**N=371**	**N=368**
Clinical Status at EOT				
Success	236 (81.9)	247 (86.7)	329 (88.7)	315 (85.6)
Failure	38 (13.2)	29 (10.2)	32 (8.6)	33 (9.0)
Indeterminate (due to missing data)[a]	14 (4.9)	9 (3.2)	10 (2.7)	20 (5.4)
Investigator Assessment of Clinical Response at EOT				
Success	260 (90.3)	262 (91.9)	342 (92.2)	332 (90.2)
Failure	16 (5.6)	9 (3.2)	16 (4.3)	19 (5.2)
Indeterminate (due to missing data) [a]	12 (4.2)	14 (4.9)	12 (3.2)	17 (4.6)

[a] Indeterminate was a subset of the response of 'Failure," if any data used to determine clinical success or failure were missing.

Patients were defined to have an indeterminate outcome if any data needed to determine whether the outcome was success or failure were missing. In order to address an imbalance in the numbers of indeterminate subjects, a multiple imputation analysis was performed on the ITT outcome. In Study DUR001-301, this analysis resulted in an adjusted treatment difference of -3.3% and a lower limit of -9.1%. Similarly, for Study DUR001-302, the same

multiple imputation analysis resulted in an adjusted treatment difference of -0.6% and a lower limit of -3.9%.

1.7.1.6 Subgroup Analyses

CLINICAL EFFICACY BY TYPES OF INFECTION IN THE ITT AND CE-EOT POPULATIONS

Across the 2 ABSSSI trials, clinical response for the relevant types of infection at the early assessment and EOT timepoints were similar between the 2 treatment groups (Section 6.7.7, Table 44). In the analysis that pooled data from the 2 studies, at the 48-72 hour timepoint, clinical response rates for patients in the ITT population with cellulitis treated with dalbavancin or comparator were 79.4% and 77.1% , respectively. Similarly, response rates for patients with a major abscess were 81.6% and 86.1%, respectively, and those with a traumatic wound/surgical site infection were 78.2% and 78.6% respectively. At EOT, the clinical response rates for patients in the CE population with cellulitis treated with dalbavancin or comparator were 90.7% and 91.7%, respectively. Similarly, response rates for patients with a major abscess were 94.0% and 95.7%, respectively, and those with a traumatic wound/surgical site infections were 86.7% and 88.6%, respectively.

1.7.2 Clinical Microbiology Results from Phase 3 ABSSSI Clinical Trials

Early response outcomes and investigator assessed efficacy at EOT by key pathogen for pooled data from the two ABSSSI studies revealed similar efficacy rates between the treatment groups for all key pathogens as shown in Table 7. Due to the smaller sample sizes, the response rates for *S. agalactiae*, *S. dysgalactiae* and *S. anginosus* group streptococci were more variable.

Table 7. Successful Clinical Outcomes by Target Pathogen in Patients with Monomicrobial Infection, ABSSSI Trials (n/N [%] of Patients)

Baseline Pathogen	48-72 Hoursa (microITT)			End of Treatment		
	Early Response		≥ 20% Lesion Reduction		Investigator Assessmenta	
	Dalbavancin	Comparator	Dalbavancin	Comparator	Dalbavancin	Comparator
S. aureus (All)	172/208 (82.7)	169/196 (86.2)	196/208 (94.2)	182/196 (92.9)	187/191 (97.9)	171/177 (96.6)
MRSA	66/82 (80.5)	47/57 (82.5)	75/82 (91.5)	50/57 (87.7)	72/74 (97.3)	49/50 (98.0)
MSSA	106/126 (84.1)	121/138 (87.7)	121/126 (96.0)	131/138 (94.9)	115/117 (98.3)	121/126 (96.0)
S. pyogenes	16/19 (84.2)	8/14 (57.1)	17/19 (89.5)	10/14 (71.4)	19/19 (100)	12/13 (92.3)
S. agalactiae	4/7 (57.1)	2/3 (66.7)	5/7 (71.4)	2/3 (66.7)	6/7 (85.7)	1/2 (50.0)
S. dysgalactiae	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
S. anginosus group	6/9 (66.7)	9/9 (100)	8/9 (88.9)	9/9 (100)	9/9 (100)	9/9 (100)
S. anginosus	1/2 (50.0)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)
S. constellatus	3/5 (60.0)	6/6 (100)	4/5 (80.0)	6/6 (100)	5/5(100)	6/6 (100)
S. intermedius	2/2 (100)	1/1 (100)	2/2 (100)	1/1 (100)	2/2 (100)	1/1 (100)

Responses are success/total (%).
[a] Includes patients from DUR001-301 and DUR001-302 (pooled)

In the ABSSSI studies, the MIC values of dalbavancin were low and covered a narrow range, particularly for *S. aureus*. The MIC values for the majority of baseline *S. aureus* isolates were 0.06 µg/mL, with a large number of isolates with MIC=0.03 µg/mL. MIC distributions for streptococci were somewhat broader, with modes generally lower than for staphylococci. The susceptibility of the clinical trial isolates reflects what has been seen in multi-year surveillance studies (Section 7.2).

Early clinical response, whether assessed by the primary endpoint or by a ≥ 20% reduction or by clinical outcome at EOT, did not differ by MIC for dalbavancin or comparators.

Also, no organism recovered at baseline was subsequently recovered at a later timepoint with a dalbavancin MIC of ≥ 4-fold that of the initial isolate, consistent with results from the in vitro passage experiments that implied that reduction in susceptibility over time would be unlikely.

1.7.3 Patients with Bacteremia

Fourteen patients in Study DUR001-301 had documented Gram-positive bacteremia at Baseline (dalbavancin: 8 patients and vancomycin/linezolid: 6 patients) and 31 patients in Study DUR001-302 had documented Gram-positive bacteremia at baseline (dalbavancin: 20

subjects and vancomycin/linezolid: 11 subjects). All of the patients with bacteremia at Baseline who had a follow-up culture available for evaluation in the dalbavancin group had documented clearance of the bacteremia, while 2 patients in the vancomycin/linezolid group had documented persistence of bacteremia.

1.7.4 Proposed Susceptibility Interpretive Criteria

The proposed susceptibility interpretive criterion for dalbavancin for both staphylococci and streptococci is ≤ 0.25 µg/mL (Table 8). At present, as there is no evidence from the clinical data as to what constitutes resistance to dalbavancin, it is suggested that isolates with MIC > 0.25 µg/mL be considered non-susceptible.

Table 8. MIC Susceptibility Test Result Interpretive Criteria for Dalbavancin

Pathogen	Susceptible[a] (µg/mL)
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 0.25
Streptococcus pyogenes, *S. agalactiae, and S. anginosus* group (includes *S. anginosus, S. intermedius, and S. constellatus*)	≤ 0.25

[a] The current absence of data on resistant isolates precludes defining any category other than "Susceptible". If an isolate yields an MIC result other than susceptible it should be retested. If the results are other than susceptible on retest, the isolate should be submitted to a reference laboratory for confirmatory testing.

1.8 Clinical Safety

1.8.1 Overview of the Clinical Safety Database

The clinical development program was international in scope and consisted of 2092 subjects enrolled in the dalbavancin group and 1350 subjects enrolled in the comparator (active comparator or placebo) group. The phase 2/3 integrated studies, the core of the clinical database, consisted of 1786 adult patients assigned to be treated with the proposed recommended dose of dalbavancin (1000 mg IV on Day 1 and 500 mg IV on Day 8). A substantial proportion of patients in the phase 2/3 studies were enrolled from the US (64.3%), younger than age 65 (82.4%), White (78.1%), overweight (71.6%), and had ABSSSI/cSSSI (72.8%). A total of 1224 patients were treated with a comparator in the phase 2/3 integrated database; and overall, the characteristics of the comparator group were similar to the corresponding characteristics in the dalbavancin group.

Section 8 contains a detailed analysis of the safety data from the dalbavancin clinical program.

1.8.2 Summary of Adverse Events

An overall summary of adverse events (AEs) is presented in Table 9. In a pooled analysis of data from the 2 pivotal ABSSSI studies (DUR001-301/302), the overall treatment-emergent adverse event (TEAE) rate was 32.8% for patients receiving dalbavancin compared to 37.9% for patients treated with vancomycin/linezolid. Treatment-related TEAEs occurred in 12.3% of those treated with dalbavancin compared to 13.7% in those given vancomycin/linezolid.

Serious AEs, both all-cause and treatment-related, were uncommon and occurred at a similar rate in each treatment regimen as did discontinuations due to a TEAE. One subject treated with dalbavancin died compared to 7 given vancomycin/linezolid. None of the deaths was considered related to drug.

Safety data from the overall phase 2/3 database demonstrated an AE profile similar to those data from the 2 pivotal ABSSSI studies. Comparator agents in the phase 2/3 population primarily included vancomycin, with a mean duration of dosing of 5 days, cefazolin, linezolid and oxacillin.

Table 9. Summary of Adverse Events: ABSSSI Studies DUR001-301/302 (pooled) and Overall Phase 2/3

	Phase 3 DUR001-301/302 Integrated Analysis Set		Phase 2/3 Integrated Analysis Set	
Number (%) of Subjects with:	**Dalbavancin (N=652)**	**Comparator (N=651)**	**Dalbavancin (N=1778)**	**Comparator (N=1224)**
Any TEAE	214 (32.8)	247 (37.9)	799 (44.9)	573 (46.8)
Any Treatment-related TEAE	80 (12.3)	89 (13.7)	328 (18.4)	246 (20.1)
Any SAE	17 (2.6)	26 (4.0)	109 (6.1)	80 (6.5)
Any Treatment-related SAE	2 (0.3)	4 (0.6)	3 (0.2)	9 (0.7)
Discontinuations from Study Drug Due to TEAE	14 (2.1)	13 (2.0)	53 (3.0)	35 (2.9)
Withdrawals from Study Due to TEAE	0	0	17 (1.0)	6 (0.5)
Deaths	1 (0.2)	7 (1.1)	10 (0.6)	14 (1.1)

Note: Treatment-related AEs are defined as those reported as possibly or probably related to study treatment or AEs for which the relationship was missing. Adverse events with missing intensity are considered severe. For summarizations of number of subjects, subjects are only counted once; for number of AE summarizations, subjects may be counted multiple times, according to the number of AEs experienced. Percentages of total number of treatment-related AEs and SAEs are based on total number of AEs.
Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event

1.8.3 Treatment-related Serious Adverse Events (SAEs)

All treatment-related SAEs from the phase 2/3 program are summarized in Table 10. Three patients treated with dalbavancin had an SAE considered by the investigator to be related to study drug: 1 patient with leukopenia, 1 with cellulitis, and 1with an anaphylactoid reaction. On the comparator regimens, 9 SAEs were considered by the investigator to be related to study drug, including 2 related to bone marrow suppression in patients receiving linezolid, and 2 cases of acute renal failure in patients receiving vancomycin.

Table 10. Treatment-Related SAEs: Integrated Phase 2/3 Studies

AE Preferred Term	Patients, n (%)	
	Dalbavancin N=1778	Comparator N=1224
≥ 1 treatment-related SAE	3 (0.2)	9 (0.7)
Leukopenia	1 (0.1)	0
Pancytopenia	0	1 (0.1)
Thrombocytopenia	0	1 (0.1)
Anaphylactoid reaction	1 (0.1)	0
Cellulitis	1 (0.1)	1 (0.1)
Gastrointestinal disorder	0	1 (0.1)
Face edema	0	1 (0.1)
Nephropathy toxic	0	1 (0.1)
Renal failure acute	0	2 (0.2)
Pancreatitis acute	0	1 (0.1)

One of these treatment-related SAEs, a life-threatening anaphylactoid reaction that led to interruption of treatment, but resolved quickly with standard medical treatment, required expedited reporting to regulatory authorities. The narrative summary of this event is described in Section 8.4.4.

1.8.4 Common Treatment-Emergent Adverse Events

Commonly-reported TEAEs with an incidence of > 2% in either treatment group are summarized in Table 11. The incidences of these types of AEs were similar between treatment groups. The most common AEs in both treatment groups were nausea, headache and diarrhea.

Table 11 Adverse Events Occurring in > 2% of Patients: Phase 2/3 Integrated Database [Number (%) of Patients]

Preferred Term	Total Dalbavancin (n = 1778)	Total Comparator (n = 1224)
Patients with at least 1 AE	799 (44.9)	573 (46.8)
Nausea	98 (5.5)	78 (6.4)
Headache	83 (4.7)	59 (4.8)
Diarrhoea	79 (4.4)	72 (5.9)
Constipation	52 (2.9)	30 (2.5)
Vomiting	50 (2.8)	37 (3.0)
Rash	38 (2.1)	22 (1.8)
Urinary tract infection	36 (2.0)	16 (1.3)
Pruritus	32 (1.8)	35 (2.9)
Insomnia	27 (1.5)	30 (2.5)

Abbreviations: AE = adverse event

1.8.5 Severity of Adverse Events

A summary of TEAEs by severity as assessed by the investigators in the phase 2/3 integrated analysis set is provided in Table 12. The majority of TEAEs were mild in severity, and the incidence of moderate and severe AEs was similar between dalbavancin and comparators.

Table 12. Overview of Treatment-Emergent Adverse Events by Maximum Intensity, Phase 2/3 Safety Population

	Patients, n (%)	
	Dalbavancin N=1778	Comparator N=1224
Subjects with ⩾ 1 TEAE	799 (44.9)	573 (46.8)
⩾ 1 mild TEAE	648 (36.4)	447 (36.5)
≥ 1 moderate TEAE	340 (19.1)	275 (22.5)
≥ 1 severe TEAE	98 (5.5)	63 (5.1)

Abbreviation: TEAE = treatment-emergent adverse event

1.8.6 Common Treatment-related Adverse Events

The incidence of TEAEs considered by the investigator to be treatment-related was low in both treatment groups (Table 13). In either the pooled analysis of patients from the two ABSSSI studies or the data from the phase 2/3 program, the treatment-related TEAEs that occurred at > 2% frequency in either treatment group were limited to nausea, diarrhea and pruritus. In each case, the incidence of these treatment-related TEAEs for patients treated with dalbavancin was similar to, or lower than, that of the comparator.

Table 13. Treatment-Related Adverse Events > 2% in any Dosing Subgroup: Studies DUR001-301/302 (pooled) and Phase 2/3

	Patients, n (%)			
	DUR001-301/302		Phase 2/3	
	Dalbavancin N=652	Comparator N=651	Dalbavancin N=1778	Comparator N=1224
Subjects with ≥ 1 Tx-related AE	80 (12.3)	89 (13.7)	328 (18.4)	246 (20.1)
Nausea	16 (2.5)	19 (2.9)	49 (2.8)	40 (3.3)
Diarrhea	5 (0.8)	16 (2.5)	45 (2.5)	45 (3.7)
Pruritus	4 (0.6)	15 (2.3)	11 (0.6)	23 (1.9)

Abbreviations: AE = adverse event; Tx = treatment

1.8.7 Treatment-Emergent Adverse Events by Demographic Groups

A summary of the incidence of TEAEs amongst phase 2/3 patients segmented by demographic characteristics is presented in Table 14. The TEAE rates, when assessed by age, gender and race were similar between dalbavancin and the comparator agents.

Table 14. Overview of Treatment-Emergent Adverse Events by Demographic Groups (Phase 2/3 Safety Population)

	Patients with ⩾ 1 TEAE, n/N (%)	
	Dalbavancin N=1778	Comparator N=1224
< 65 years of age	641/1465 (43.8)	465/995 (46.7)
⩾ 65 years of age	158/313 (50.5)	108/229 (47.2)
Male	449/1066 (42.1)	308/711 (43.3)
Female	350/712 (49.2)	265/513 (51.7)
White	579/1388 (41.7)	448/1008 (44.4)
Black or African American	90/143 (62.9)	58/88 (65.9)
Asian	25/36 (69.4)	23/41 (56.1)
American Indian or Alaska Native	1/5 (20.0)	3/4 (75.0)
Native Hawaiian/Other Pacific Islander	1/1 (100.0)	0/1 (0.0)
Other	103/205 (50.2)	41/82 (50.0)

Abbreviation: TEAE = treatment-emergent adverse event

1.8.8 Adverse Event Topics of Interest

1.8.8.1 Infusion-associated and Renal-associated Adverse Events

Adverse event topics of interest include an assessment of infusion-associated and renal-associated AEs, given that these are AEs which have been reported in patients treated with other glycopeptide antibiotics. A summary of AEs related to these 2 AE types is provided in Table 15. While the comparator group for the ABSSSI studies was one that included a large

proportion of patients who received vancomycin, there were studies in which other classes of antibiotics comprised a substantial proportion of the comparator cohort.

Table 15. Adverse Event Topics of Interest: Phase 2/3 Safety Population

	Dalbavancin N=1778	Comparator N=1224
Patients with Infusion-associated AE, n (%)	40 (2.2)	38 (3.1)
Infusion-associated events, n	48	--
Events on day of active infusion, n	12	--
Renal-associated AE, n (%)	33 (1.9)	24 (2.0)
Treatment-related renal-associated AE, n (%)	3 (0.2)	5 (0.4)

Abbreviation: AE = adverse event

A smaller proportion of dalbavancin treated patients had an infusion-related AE relative to those treated with a comparator agent. None of the reports of infusion site-associated AEs was considered an SAE. Of note, given the double-blind nature of these trials, many dalbavancin patients retained an IV catheter even on days when they were not receiving dalbavancin in order to receive daily infusions of placebo to vancomycin. Of the 48 infusion-related AEs that occurred in 40 dalbavancin-treated patients, only 12 of the infusion-associated AEs occurred on the day of a dalbavancin infusion. A detailed discussion of infusion site-associated events is presented in Section 8.4.6.4.

The incidences of patients with a TEAE in the Renal Disorders SOC were low and similar between the dalbavancin and comparator treatment groups (33 [1.9%] versus 24 [2.0%], respectively) and few events were considered by the investigator to be related to study drug (3 [0.2%] vs. 5 [0.4%], respectively).

1.8.8.2 Potential for Allergic Reacions

Allergic reactions in the integrated phase 2/3 program are summarized in Table 16. The incidence of subjects with a potential allergic reaction was low and similar between the dalbavancin and comparator treatment groups; few events were considered by the investigator to be related to study drug in the phase 2/3 integrated database. No patient in the phase 2/3 development program receiving dalbavancin experienced an AE of red man syndrome versus 2 patients (0.2%) treated with comparator.

Table 16. Potential Allergic Reactions: Phase 2/3 Safety Population

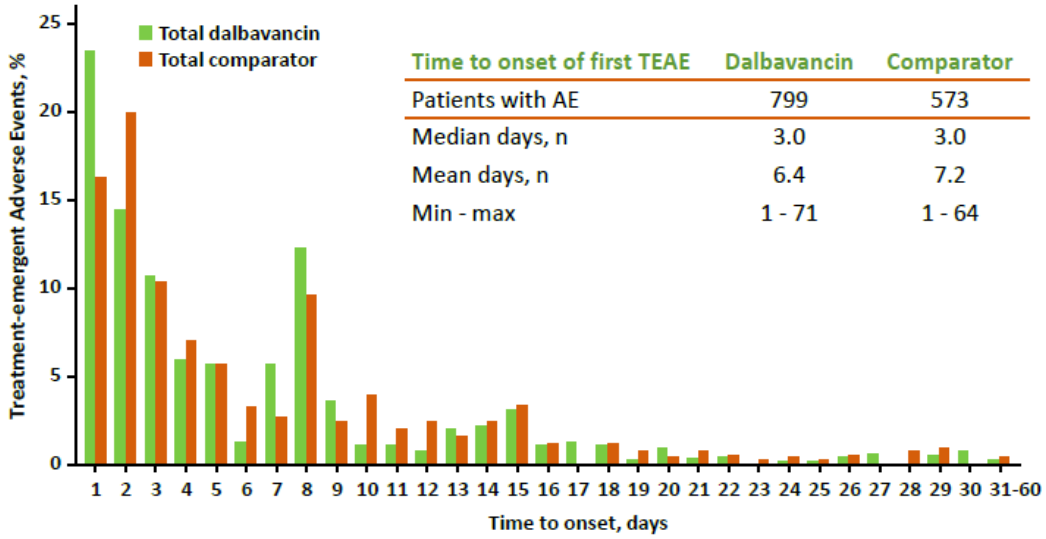
System Organ Class Preferred Term	Dalbavancin N=1778	Comparator N=1224
Immune system disorders		
Hypersensitivity	5 (0.3)	1 (0.1)
Food allergy	2 (0.1)	0
Allergic oedema	1 (0.1)	0
Anaphylactoid reaction	1 (0.1)	0
Seasonal allergy	1 (0.1)	1 (0.1)
Drug hypersensitivity	0	1 (0.1)
Skin and subcutaneous tissue disorders		
Rash	38 (2.1)	22 (1.8)
Urticaria	8 (0.4)	8 (0.7)
Rash pruritic	4 (0.2)	3 (0.2)
Rash generalized	2 (0.1)	2 (0.2)
Rash macular	2 (0.1)	2 (0.2)
Swelling face	2 (0.1)	2 (0.2)
Drug rash with eosinophilia and systemic symptoms	1 (0.1)	0
Rash erythematous	1 (0.1)	0
Rash papular	1 (0.1)	1 (0.1)
Rash maculo-papular	0	1 (0.1)
Red man syndrome	0	2 (0.2)

1.8.9 Onset and Duration of Adverse Events

1.8.9.1 Day of Onset of Adverse Events

An overview of the time (day) of onset of AEs is described in Figure 8. The onset of the majority of AEs were reported in the early part of the study period. Late onset AEs were seen at similar rates in patients treated with dalbavancin relative to those receiving a comparator agent. The median (3.0 days each) and mean (6.4 vs. 7.2 days) day of onset of the first AE was similar for both dalbavancin and comparator treatment groups.

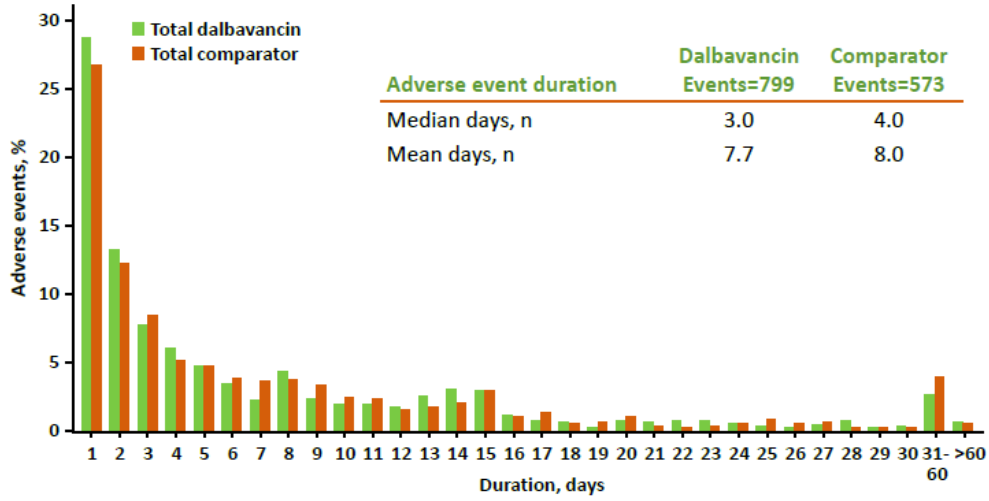
Figure 8. Day of Onset of Treatment-Emergent Adverse Events: Phase 2/3 Integrated Safety Database



1.8.9.2 Duration of Adverse Events

An overview of the time (day) of onset of AEs is described in Figure 9. The distribution of the duration of AEs in patients receiving dalbavancin was similar to that for patients given the comparator regimens. The median (3.0 and 4.0 days) and mean (7.7 and 8.0) duration of AEs was similar for both dalbavancin and comparator treatment groups. This observation is especially important for a drug with a long half-life such as dalbavancin, where a thorough understanding of the duration and time to onset of AEs is relevant and important.

Figure 9. Duration of Treatment-Emergent Adverse Events: Phase 2/3 Integrated Safety Database



1.8.10 Summary of Clinical Laboratory Changes

A summary of laboratory analyses throughout the phase 2/3 clinical program is described in Table 17. Clinical laboratory parameters were monitored carefully throughout the development program. Results of these laboratory parameters were analyzed utilizing multiple methods such as analyses evaluating all post-baseline laboratory abnormalities that would be considered potentially clinically significant, PCS (eg, hemoglobin < 0.8% of lower limit of normal [LLN]), abnormal laboratory values that were also potentially clinically significant changes (PCSC) from baseline (eg, ALT ≥ 3 times upper limit of normal that is also a 3-fold increase from the baseline value) and shift analyses that evaluate the proportion of patients with a normal laboratory parameter at baseline who develop abnormalities on or after study drug therapy versus those who had abnormal laboratory parameters at baseline.

Table 17. Clinical Laboratory Values, Phase 2/3 Safety Population

Clinical laboratory parameter (potentially clinical significant criteria)	Patients, n (%)			
	On Treatment		End of Treatment	
	Dalbavancin	Comparator	Dalbavancin	Comparator
Hematocrit (≤ 0.8×LLN and ≥ 0.25-fold ↓)	5 (0.4)	6 (0.7)	5 (0.3)	4 (0.4)
Platelets (⩽ 0.6×LLN and ⩾ 0.4-fold ↓)	7 (0.6)	7 (0.8)	2 (0.1)	4 (0.4)
WBC (⩽ 0.5×LLN and ⩾ 0.75-fold ↓)	2 (0.2)	2 (0.2)	1 (0.1)	1 (0.1)
ALT (⩾ 3×ULN and ⩾ 3-fold ↑)	6 (0.5)	1 (0.1)	6 (0.4)	3 (0.3)
AST (⩾ 3×ULN and ⩾ 3-fold ↑)	8 (0.6)	1 (0.1)	3 (0.2)	3 (0.3)
Alkaline phos (⩾ 1.5×ULN and ⩾ 2-fold ↑)	8 (0.6)	4 (0.4)	9 (0.6)	6 (0.6)
Total bilirubin (⩾ 1.5×ULN and ⩾ 3-fold ↑)	1 (0.1)	0	2 (0.1)	1 (0.1)
Creatinine (> 1.5×ULN and > 2-fold ↑)	1 (0.1)	2 (0.2)	3 (0.2)	6 (0.6)

Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal; WBC = white blood cell count; ALT = alanine aminotransferase; AST = aspartate aminotransferase

Overall, no significant difference in laboratory safety assessments between dalbavancin and comparators was observed. No cases of Hy's law occurred in the entire development program. A slightly higher proportion of patients in the dalbavancin group was noted to have elevated serum aminotransferases on treatment relative to patients treated with a comparator agent (ALT ≥ 3x ULN and 3-fold increase: 0.5% in the dalbavancin group vs 0.1% in the comparator group; AST ≥ 3x ULN and 3-fold increase: 0.6% in the dalbavancin group vs 0.1% in the comparator group). However, this difference disappeared at the end of therapy (ALT ≥ 3x ULN and 3 fold increase: 0.4% in the dalbavancin group vs 0.3% in the comparator group; AST ≥ 3x ULN and 3-fold increase: 0.2% in the dalbavancin group versus 0.3% in the comparator group). A slightly higher proportion of patients in the comparator group was observed to have elevated serum creatinine at the end of therapy (serum creatinine ≥ 1.5x ULN and 2-fold increase: 0.2% in the dalbavancin group vs 0.6% in the comparator group).

Given that the liver was identified as a target organ in non-clinical toxicology studies and the slight increase noted in serum aminotransferases for patients in the dalbavancin group in the Phase 2/3 development program, a thorough analysis of all hepatobiliary parameters was conducted. Overall, the clinical development program for dalbavancin provides a substantial database for drug exposure, with treatment of over 1600 subjects and rigorous monitoring of hepatobiliary function, that allows for an adequate assessment of dalbavancin's impact on hepatobiliary function. The frequency of patients with a very high level (≥10x ULN) of aminotransferases noted post-Baseline was extremely low and similar between treatment groups (3 subjects in each treatment group). There was no evidence of altered liver function accompanying or promptly following elevation of aminotransferases such as an increase in serum total bilirubin unexplained by other causes. No case of Hy's law was seen in the dalbavancin clinical program. Furthermore, the proportion of cases with aminotransferase elevations to ≥ 3x ULN in the dalbavancin group was comparable to that seen in the comparator group. Thus, based on the *FDA Guidance for Industry: Drug Induced Liver Injury: Premarketing Clinical Evaluation* (July 2009), dalbavancin has a low potential for causing severe drug-induced liver injury.

The kidney was identified as a target organ in nonclinical studies (Section 4.3.4.1), and renal effects were carefully monitored in the clinical program. In the phase 2/3 integrated analysis set, the frequency of AEs in the renal disorder SOC was similar in the dalbavancin and comparator groups (1.9% vs. 2.0%). Treatment-related renal disorder AEs (0.2% vs. 0.4%) and serious renal disorder AEs (0.2% vs. 0.5%) were similar in the dalbavancin and comparator groups, respectively. Systematic review of renal laboratory test parameters, including BUN and serum creatinine, did not suggest nephrotoxicity in patients treated with dalbavancin.

1.9 Benefit Versus Risk Conclusions

There is an increasing medical need for new efficacious and safe antibacterial agents with enhanced Gram-positive activity. Recently approved agents for the treatment of SSSIs such as quinopristin/dalfopristin (Nichols 1999; Lamb 1999; Rubinstein 1999; Eliopoulos 2003), linezolid (Stevens 2000; Clemett 2000; Perry 2001), daptomycin (Arbeit 2004; Carpenter 2004), tigecycline (Doan 2006), telavancin (Stryjewski 2008), ceftaroline fosamil (Saravolatz 2011), and teicoplanin (Stevens 1999) have limitations, such as inhibition of hepatic CYP3A4, myelosuppression, allergies to beta-lactams, twice-daily IV dosing, the requirement for an altered dosing regimen in renal failure, and nephrotoxicity and reproductive toxicity. The Infectious Diseases Society of America (IDSA) has cited the need for a multi-pronged approach to address the impact of antibiotic resistance. In its 2004 white paper, *Bad Bugs, No Drugs*, there is stated concern about decreased research and development activity (IDSA 2004). Furthermore, there has been an increase in the proportion of staphylococcal infections due to MRSA versus MSSA. This increase is apparent in community-acquired infections and in the hospital, particularly in the intensive care unit, where the proportion of such infections may approach 70% in some institutions (National Nosocomial Infection Surveillance 2003), and is greater than 50% even in some outpatient settings (King 2006).

The following conclusions may be drawn regarding benefits and risks of dalbavancin versus approved therapies:

- Dalbavancin exhibits a favorable benefit/risk profile when compared with approved Gram-positive antibacterial agents.
- Dalbavancin's efficacy rate in the treatment of ABSSSI is high, as a result of its antibacterial potency, PK profile and tissue penetration data. The severity of illness of patients enrolled in the pivotal Phase 3 studies was high, based on lesion size, the incidence of fever at baseline, elevated WBC counts, elevated hs-CRP and SIRS criteria.
- The PK profile demonstrates low inter-individual variability; therapeutic drug monitoring is not required.
- The once-weekly dosing regimen avoids the potential pitfalls of patient noncompliance with oral medication, and reduces the requirement for long-term hospital stays, with its accompanying need for daily intravascular access, and attendant risks of line-related thrombosis and infection; there is no requirement for an oral formulation to allow step-down therapy.
- Continuous bactericidal activity against streptococci and staphylococci, including MRSA throughout the dosing period contributes to the high and sustained clinical outcomes observed in clinical trials.
- Dalbavancin exhibits favorable tolerability and safety compared with alternatives in the following areas:
  - no teratogenicity effects were observed, nor were immunotoxicity effects at doses approximating human therapeutic concentrations,
  - no demonstrated signal of thrombocytopenia in vitro or in vivo,
  - no interference with CYP450 enzymes, reducing the risk of drug-drug interactions,
  - low risk of infusion-related toxicity at a 30-minute infusion time,
  - no demonstrated risk of nephrotoxicity in human trials,
  - no dosage adjustment needed for body mass index; dose adjustment is only required at the initiation of treatment based on $CL_{CR} < 30$ mL/min,,
  - no therapeutic drug monitoring is required,
  - low incidence of nausea and vomiting,
  - no signal for muscle or peripheral nerve toxicity,
  - hepatic, CNS, and GI safety profiles appear to be similar to those of marketed anti-Gram-positive antibacterials,
  - no effect of dalbavancin on the QT interval.
- The potential for resistance to dalbavancin appears to be low, based on results from both nonclinical in vitro studies and clinical trials.

The data from the phase 3 pivotal clinical studies provide robust confirmation of the efficacy of dalbavancin for the treatment of ABSSSI caused by Gram-positive bacteria, including infections due to MRSA. Efficacy was high and consistent in all infection subtype categories. Overall patient management by health care providers and caregivers in inpatient

or outpatient settings would be expected to be facilitated with the 2-dose regimen versus a minimum of 14-20 infusions in a 7-10 day course of conventional antibacterial therapy. Additionally, the use of only 2 infusions 1 week apart may eliminate the need for subsequent continuation on oral antibiotic therapy (a situation in which patient compliance can be an issue), and reduce the need for daily outpatient IV therapy, all without compromising either clinical efficacy or safety relative to approved agents.

LIST OF ABBREVIATIONS

ABSSSI	acute bacterial skin and skin structure infections
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANS	autonomic nervous system
APD	action potential duration
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
ATCC	American Type Culture Collection
AUC/MIC	area under the plasma-concentration curve over minimal inhibitory concentration
β HS/B HS	β-hemolytic streptococci
BMI	body mass index
BSA	body surface area
CA	community-acquired
CE	clinically evaluable
CE-EOT	clinically evaluable population at end of treatment
CE-SFU	clinically-evaluable population at short term follow-up
CFU	colony-forming units
CI	confidence interval
CL	clearance
CL_{CR}	creatinine clearance
CLSI	Clinical and Laboratory Standards Institute
CoNS	coagulase-negative staphylococci
C_{max}	peak plasma concentration
CNS	central nervous system
CRBSI	catheter-related bloodstream infections
CSF	cerebrospinal fluid
CSR	clinical study report
cSSSI	complicated skin and skin structure infections
%CV	percent coefficient of variation
CYP450	cytochrome P450
D5W	5% dextrose injection solution
DBP	diastolic blood pressure
ECG	electrocardiogram
ESRD	end stage renal disease
EOT	end of treatment
EU	European Union

EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GISA	glycopeptide-intermediate *Staphylococcus aureus*
HA	hospital-acquired
HCT	hematocrit
hERG	human ether-à-go-go-related gene
Hgb	hemoglobin
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
hs-CRP	high-sensitivity C-reactive protein
hVISA	heteroresistant vancomycin-intermediate *Staphylococcus aureus*
I	intermediate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSA	Infectious Diseases Society of America
IEC	independent ethics committee
IHMA	International Health Management Associates
IND	investigational new drug application
IRB	institutional review board
ISE	Integrated Summary of Efficacy
ITT	Intent-to-treat
IV	intravenous(ly)
LFU	long term follow-up
MAG	mannosylaglycone
MBC	minimum bactericidal concentration
MDR	multidrug-resistant
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimal inhibitory concentration
MicroITT	microbiological intent-to-treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MRSE	methicillin-resistant Staphylococcus epidermidis
MSSA	methicillin-susceptible *Staphylococcus aureus*
MTD	maximum tolerated dose
NC	not calculated
NDA	New Drug Application
NI	noninferior(ity)
NOAEL	no observed adverse effect level
NOEL	no observed effect level

NS	non-susceptible
OH-dalbavancin	hydroxydalbavancin
P-80	polysorbate-80
PCS	potentially clinically significant
PCSC	potentially clinically significant change
PDUFA	Prescription Drug User Fee Act
PICC	peripherally inserted central catheter
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PO	orally; by mouth (Lat.: *per os*)
Pop	analysis population
RBC	red blood cells/count
q4h	every 4 hours
Q6h	every 6 hours
Q12h	every 12 hours
QC	quality control
QIDP	qualified infectious disease product
QT (interval)	time from the beginning of the QRS complex to the end of the T wave on the electrocardiogram
QT_cF	QT interval corrected for heart rate using Fridericia's (QTcF) formula
R	resistant
ROW	rest-of-world
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SFU	short term follow-up
SIRS	systemic inflammatory response syndrome
SOC	system organ class
sp./spp.	species
SPA	special protocol assessment/agreement
SBP	systolic blood pressure
SSSI	skin and skin structure infections
S	susceptible
T>MIC	time above minimal inhibitory concentration
$t_{1/2}$	β half-life
$T_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time to peak plasma concentration
TMP/SMX	trimethoprim/sulfamethoxazole
TOC	test of cure
TP	time point

Tx	treatment
US(A)	United States (of America)
USP	United States Pharmacopoeia
uSSSI	uncomplicated skin and skin structure infections
V_d	volume of distribution
VGS	viridans Group streptococci
VISA	vancomycin intermediate *Staphylococcus aureus*
VRE	vancomycin-resistant enterococci
VRSA	vancomycin-resistant *Staphylococcus aureus*
V_{ss}	volume of distribution at steady state
WBC	white blood cell/count

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2 INTRODUCTION

2.1 Acute Bacterial Skin and Skin Structure Infections: Medical Need

The increasing incidence of infections caused by antibiotic-resistant bacteria is a worldwide phenomenon. Resistance is occurring across many Gram-positive genera, including staphylococci, streptococci and enterococci; methicillin-resistant staphylococci, penicillin-resistant *S. pneumoniae*, and vancomycin-resistant enterococci (VRE) are of particular interest (Jones 2003; Diekema 2004).

In particular, MRSA has become a major concern, not just with respect to hospital-acquired infections (HA), but also because a community acquired (CA) variant has appeared, unrelated to the hospital-acquired strains (Salgado 2003; Daum 2007). Most CA-MRSA strains produce skin and skin structure infections (SSSIs), which include wound infections, abscesses and cellulitis (Gorak, et al, 1999). CA-MRSA is the most common cause of CA soft tissue infections at major clinical care centers (Moran 2005). Furthermore, infection by *S. aureus* strains with the methicillin-resistance phenotype has been associated with a poor clinical outcome as compared to that with susceptible isolates (Engemann 2003; Melzer 2003). In addition to MRSA, glycopeptide-intermediate *S. aureus* (GISA) and glycopeptide-resistant enterococci (VRE or GRE), particularly *E. faecium*, are of additional concern for treatment of these infections. This changing epidemiology is global in scope, and has led to an increasing need to administer IV antibacterial agents in a hospital and/or clinic setting with a spectrum of activity targeted for the empirical treatment of acute bacterial SSSI (Dieckema 2004; Jones 2003; Moellering 2006; Abrahamian 2008).

While a recent trend has shown the overall incidence of healthcare-acquired infections involving MRSA to be decreasing (Kallen 2010), additional therapies are needed to mitigate these serious infections caused by multidrug-resistant organisms, while reducing the burdens to healthcare providers and caregivers, as well as pain and discomfort to patients for requiring 10 to 14 days of treatment involving multiple daily drug administrations in hospital or outpatient clinic settings. Until the approval of antibiotics such as linezolid, tigecycline and daptomycin, glycopeptides such as vancomycin (global) and teicoplanin (outside the United States) were the only available options for treating most serious infections due to methicillin resistant strains. However, concerns over the clinical response to therapy with these antibiotics for staphylococcal isolates with MICs at the upper end of the susceptible range, combined with their pharmacodynamic and clinical shortcomings, and the increasingly important role of Gram-positive bacterial infections in the clinical setting, have motivated the development of newer agents. While the newer antibiotics have excellent activity against Gram-positive pathogens, they have specific limitations: linezolid is contraindicated in patients who are using selective serotonin uptake inhibitors and is associated with bone marrow suppression; the product labeling for tigecycline was recently updated to include information regarding increased mortality associated with its use; daptomycin is associated with concerns regarding rhabdomyolysis and the emergence of resistance on therapy; telavancin is associated with nephrotoxicity and reproductive toxicity; and ceftaroline requires IV access for twice daily administration over many days.

An antibacterial agent that offers benefits of comparable efficacy, with comparable or better safety, but with a more simplified dosing regimen, may provide additional benefits to ensure compliance with therapy while minimizing the burden on health care providers and reducing the need for prolonged hospital stays and for multiple venipunctures or indwelling venous catheters with their inherent risks of secondary infections and local discomfort.

2.2 Dalbavancin: Development and Regulatory History

2.2.1 Sponsorship History of Dalbavancin

Several corporate entities have contributed to the development history of dalbavancin. It was originally developed for clinical use by Marion Merrell Dow, which later reorganized as Biosearch Italia. Following the First in Human PK study conducted in the United Kingdom (1999), Biosearch Italia then partnered with Versicor Pharmaceuticals, Inc. (a biopharmaceutical company in the United States), who submitted the IND to begin US trials (2000). The firm later merged with Versicor, forming Vicuron Pharmaceuticals, Inc. (2003). Versicor/Vicuron performed all initial phase 1-3 clinical trials for dalbavancin, and originally submitted NDA 021-883 on December 21, 2004, prior to its acquisition by Pfizer Inc. (September 2005). Pfizer divested of Vicuron Pharmaceuticals and dalbavancin to Durata Therapeutics, Inc., in December 2009.

2.2.2 United States Regulatory History of Dalbavancin

Dalbavancin was granted Fast Track Status by the FDA in November 2003 for study in the treatment of serious skin infections caused by Gram-positive bacteria.

The initial clinical development of dalbavancin by Versicor/Vicuron/Pfizer was performed in concordance with standard approaches as used for the evaluation of newer antibacterial agents and guidances for Good Clinical Practice. All clinical studies were subject to regular monitoring by the Sponsor or an appointed Contract Research Organization.

The initial NDA submission contained 4 phase 2/3 trials in the treatment of skin and skin structure infections (SSSI), which included 1 pivotal phase 3 trial in patients with complicated skin and skin structure infections (cSSSI, VER001-9) and 1 supportive phase 3 trial in patients with uncomplicated skin and skin structure infections (uSSSI,VER001-8), 2 other smaller, phase 2/3 trials in SSSI (VER001-5 and VER001-16), and a 5th trial, VER001-4, a phase 2 study in catheter-related blood stream infections (CRBSI). cSSSI was the only targeted indication sought by Vicuron in the initial NDA submission.

Shortly after the acquisition of Vicuron by Pfizer, NDA 021-883 received the first of 3 Approvable Letters from the FDA (September 2005). The 2nd Approvable Letter was received in June 2006, and the 3rd was received in December 2007. The first 2 Approvable Letters focused on pending issues related to manufacturing. The pivotal study VER001-9 was considered adequate and well-controlled, and served as the basis of a positive benefit risk assessment, supported by the safety and efficacy data available in the other clinical trials. The 3rd Approvable letter contained comments related to the Agency's evolving thinking on clinical trial design for SSSI, in particular, the non-inferiority margin for uSSSI in supportive

Study VER001-8. Pfizer provided complete responses to all 3 Approvable Letters, but later withdrew the Application in September 2008 for reasons unrelated to safety or efficacy.

Prior to the issuance by FDA of the new draft *Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment* (August 2010), Durata initiated End-of phase 2 dialog with the DAIP regarding the conduct of a new phase 3 trial under the new draft Guidance-compliant indication, ABSSSI. It was expected that the cSSSI study VER001-9 would constitute the 1st adequate and well-controlled trial, and that a second, Guidance-compliant trial (DUR001-301) would be the 2nd pivotal trial to support registration. Durata subsequently chose to perform a second new trial, of identical design to DUR001-301, believing it would enhance the clinical package now targeting the new early clinical endpoint. The Division agreed with this decision. These 2 trials were identified as DUR001-301 and DUR001-302. The 2 trial protocols were the subject of Special Protocol Assessment agreements (SPA) with the Agency in 2010 and 2011, respectively. These trials began accruing patients worldwide in March 2011 and completed enrollment by December 2012.

In October 2012, dalbavancin obtained Qualified Infectious Disease Product designation (QIDP) under the GAIN Act statute [Title VIII of the Food and Drug Safety and Innovation Act of 2012 (FDASIA)] for a product with the potential for treating serious/life-threatening infections caused by resistant bacterial pathogens, including MRSA. Such a designation provides for a classification of the Application for Priority Review.

Following pre-NDA meetings in June-July 2013, in which Durata reviewed the results of the 2 pivotal clinical trials, an updated version of NDA 021-883 was submitted on September 26, 2013. The Application was accepted for review on November 25, 2012, and in accordance with the provisions of the GAIN Act statute, the Agency assigned a Priority Review classification, with a user fee goal date of May 26, 2014.

On February 12, 2014, the FDA announcement of the March 31, 2014 meeting of the Anti-Infectives Advisory Committee for the purpose of review of this Application appeared in the Federal Register (Department of Health and Human Services 12 February 2014).

3 CHEMISTRY AND PHARMACEUTICAL INFORMATION

3.1 Drug Substance

Dalbavancin, a hydrochloride salt, is a lipoglycopeptide antibiotic that is obtained by chemical modification of a natural glycopeptide, A-40,926, a fermentation product of *Nonomuraeae* sp. Dalbavancin drug substance, a hydrochloride salt, is a mixture of 5 closely-related homologs (A_0, A_1, B_0, B_1, and B_2).

The major homolog (≥80%) is designated B_0. Its chemical name, as the free base, is 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-O-[2-deoxy-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronosyl]-38-[[3-(dimethylamino)propyl]carbamoyl]-42-O-α-D-mannopyranosyl-15-N-methyl(ristomycin A aglycone). The 5 homologs share the same core structure and differ from one another in the length and/or branching of their respective fatty acid side chains on the N-acylaminoglucuronic acid moiety (R_1), and/or the presence of an additional methyl group on the N-terminus of the peptide (R_2). The structural formula of the dalbavancin homolog series is shown in Figure 10, and the structural variation in homologs is presented in Table 18.

In addition to the B_0 homolog, whose relative abundance is controlled by manufacturing specification, the other 4 homologs are produced to controlled specifications in the final active pharmaceutical ingredient (API) mixture. The in vitro antibacterial activity of the 5 drug substance homolog components are similar.

Figure 10 Structural Formula of Dalbavancin

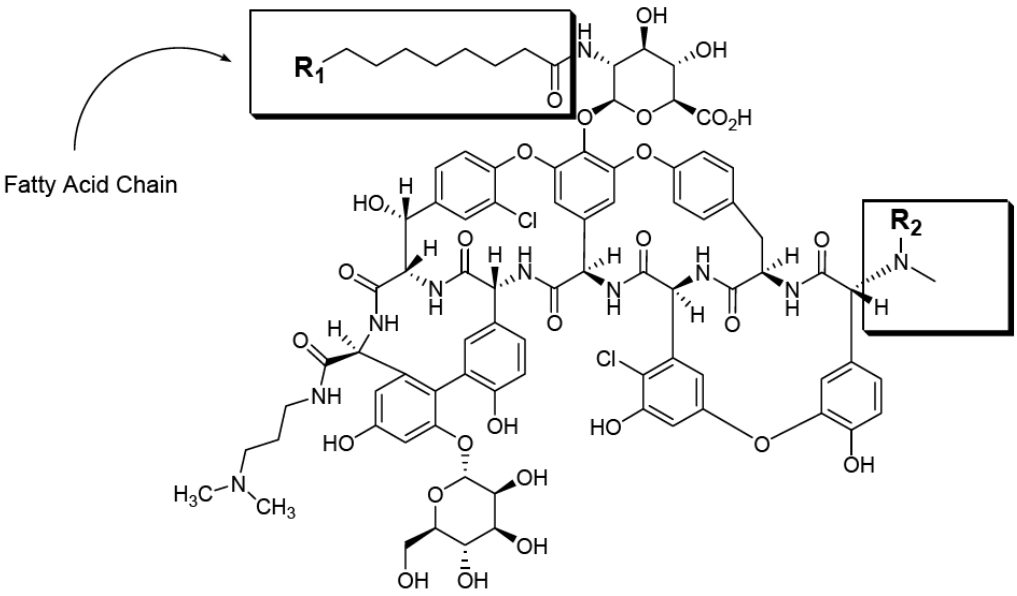


Table 18 Substitution Patterns for Dalbavancin API Homologs

Dalbavancin Homolog	R_1	R_2	Molecular Formula	Molecular Weight[a]	Relative Abundance in API
A_0	$CH(CH_3)_2$	H	$C_{87}H_{98}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1802.7	Controlled by specification
A_1	$CH_2CH_2CH_3$	H	$C_{87}H_{98}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1802.7	
B_0	$CH_2CH(CH_3)_2$	H	$C_{88}H_{100}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1816.7	≥80%
B_1	$CH_2CH_2CH_2CH_3$	H	$C_{88}H_{100}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1816.7	Controlled by specification
B_2	$CH_2CH(CH_3)_2$	CH_3	$C_{89}H_{102}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1830.7	

[a] Anhydrous free base

Abbreviation: API = active pharmaceutical ingredient

3.2 Drug Product

Description and Preparation for Adminstration

Dalbavancin for Injection is available in glass vials containing dalbavancin hydrochloride equivalent to 500 mg dalbavancin free base as a sterile, lyophilized, white to off-white to pale yellow, preservative-free solid, which must be reconstituted with 25 mL of sterile water for injection and subsequently diluted with 5% dextrose injection (D5W) to a final concentration of 1 to 5 mg/mL prior to IV administration. Dalbavancin should not be diluted with solutions other than 5% Dextrose Injection, USP. Saline-based infusion solutions may cause precipitation and should not be used.

Detailed instructions for reconstitution and dilution are described in the proposed product labeling.

Reconstitution: Dalbavancin for Injection must be reconstituted under aseptic conditions, using 25 mL of Sterile Water for Injection, USP, for each 500 mg vial. To avoid foaming, alternate between gentle swirling and inversion of the vial until its contents are completely dissolved. Do not shake. The reconstituted vial contains 20 mg/mL dalbavancin as a clear, colorless to yellow solution, with a pH of 4.0 to 5.0.

Dilution: Aseptically transfer the required dose of reconstituted dalbavancin solution from the vial(s) to an IV bag or bottle containing 5% Dextrose Injection, USP. The diluted solution must have a final dalbavancin concentration of 1 to 5 mg/mL. The final pH of the diluted solution is similar to that of the reconstituted solution (4.0 to 5.0). Discard any unused portion of the reconstituted solution.

Administration Instructions

Dalbavancin for Injection is administered via IV infusion over 30 minutes.

Handling and Storage

Unreconstituted dalbavancin HCl for injection should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Reconstituted vials may be stored either refrigerated at 2-8°C (36-46°F), or at controlled room temperature 20-25°C (68-77°F). Do not freeze.

Once diluted into an IV bag or bottle as described above, dalbavancin solution may be stored either refrigerated at 2-8°C (36-46°F) or at a controlled room temperature of 20-25°C (68-77°F). Do not freeze.

The total time from reconstitution to dilution to administration should not exceed 48 hours.

4 NONCLINICAL INFORMATION

4.1 Pharmacology

4.1.1 Primary Pharmacodynamics

4.1.1.1 Mechanism of Action

Dalbavancin has the same mechanism of action as other glycopeptide antibacterial agents, such as vancomycin and telavancin, ie, interfering with cell wall synthesis mediated by binding to the D-ala-D-ala terminus of the stem pentapeptide present in nascent peptidoglycan. Binding to this substrate inhibits the cross-linking reactions (transpeptidation and transglycosylation) that strengthen the cell wall.

4.1.1.2 In Vitro Antibacterial Activity

The spectrum of activity of dalbavancin includes most species of Gram-positive bacteria, and specifically those that are are important pathogens implicated in ABSSSI (principally staphylococci, streptococci and enterococci).

Prospective worldwide surveillance of the in vitro potency of dalbavancin, in comparison with other antimicrobial agents, was begun in 2002 and has continued through 2012 at the time of the preparation of this Application, with several thousand Gram-positive clinical isolates tested in most years. The emphasis has been on species that are relevant to the proposed indication, including MRSA and multidrug-resistant (MDR) staphylococcal isolates. Additionally, the potency of dalbavancin against collections of specific organism categories was examined in a number of studies.

Dalbavancin MIC ranges for aerobic Gram-positive cocci were very narrow, with MIC_{90} (MIC for at least 90% of strains tested) ranging from ≤0.03 to 0.12 µg/mL for most species. Dalbavancin demonstrated greater in vitro potency than currently available glycopeptides and most other comparators. The activity of dalbavancin is not affected by resistance to other classes of antibacterial agents.

Dalbavancin demonstrates greater in vitro potency against some organisms that are resistant to vancomycin or teicoplanin, including coagulase-negative staphylococci (CoNS) resistant or with reduced susceptibility to teicoplanin. In one study of 25 vancomycin-intermediate (VISA) and heteroresistant vancomycin-intermediate *S. aureus* isolates (hVISA), all MIC values of dalbavancin were ≤ 1 µg/mL. In other studies, dalbavancin MICs for 36 hVISA strains were 0.03-0.12 µg/mL (Campanile 2010), and heterogeneous resistance to dalbavancin was not detected among 32 MRSA strains, including both vancomycin-susceptible and hVISA strains. In a study of 20 isolates of CoNS with reduced susceptibility to teicoplanin (MIC > 8 µg/mL), dalbavancin MIC values were 0.03-0.12 µg/mL. Among > 7,000 CoNS isolates from the SENTRY data base, which included approximately 10% of isolates considered to be teicoplanin-resistant by EUCAST criteria, all isolates were susceptible to ≤ 1 µg/mL of dalbavancin and 99.6% of all isolates were susceptible to ≤ 0.25 µg/mL. Resistance to dalbavancin among Gram-positive bacteria appears to be limited to certain intrinsically glycopeptide-resistant species and to bacteria expressing the

VanA phenotype of acquired resistance. Dalbavancin is active against the intrinsically vancomycin-resistant enterococcal species expressing the VanC phenotype and against VanB strains with acquired resistance, but is not active against other intrinsically glycopeptide-resistant Gram-positive species such as pediococci, leuconostocs and some species of lactobacilli. Like other glycopeptides, dalbavancin is not generally active against Gram-negative bacteria; however in vitro activity against certain fastidious Gram-negative species such as *Neisseria gonorrhoeae* and *Moraxella catarrhalis* has been reported.

With the exception of the very rare vancomycin-resistant *S. aureus* (VRSA) strains, no staphylococci or streptococci resistant to dalbavancin have been detected among thousands of isolates from surveillance studies and dalbavancin clinical trials. Additionally, no emergence of resistance to dalbavancin was detected in animal infection experiments or in vitro studies designed to detect development of resistance or heterogeneous susceptibility. Thus, the potential for emergence of resistance to dalbavancin in target organisms appears to be low.

Dalbavancin is bactericidal in vitro for staphylococci and streptococci at free drug concentrations that are sustained in patients treated with the proposed human therapeutic regimen. The bactericidal activity of dalbavancin in vitro is time-dependent. While the in vitro activity of dalbavancin is affected by the addition of serum, its inhibitory and bactericidal activities are evident at concentrations lower than the concentrations of free drug that are maintained over the entire dosage interval with the proposed regimen; due to the long β $t_{1/2}$ of dalbavancin in humans (8.5 days), bactericidal concentrations are present for up to a week after administration of each dose.

In experiments in vitro with several species of bacteria, no antagonism was observed when dalbavancin was combined with other antimicrobial agents that are used to treat Gram-positive and Gram-negative infections.

The potent in vitro activity of dalbavancin against contemporary clinical isolates of Gram-positive bacteria has been confirmed in more recent studies. An overview of in vitro susceptibility studies relevant to the bacterial species in ABSSSI is described in Section 7.2.

Dalbavancin is approximately 93% protein-bound in human plasma (Section 5.2.1.2). MIC values in the presence of 50% human serum are somewhat increased, reflecting this reversible binding; however, they remain considerably lower than concentrations of dalbavancin that are maintained in human plasma throughout the 14-day dosing interval.

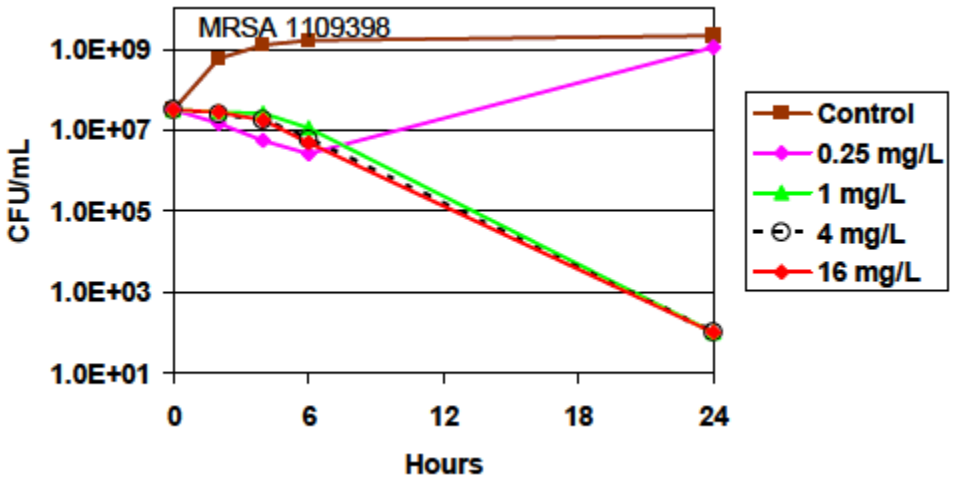
BACTERICIDAL ACTIVITY OF DALBAVANCIN

Consistent with its mechanism of action, involving interruption of cell wall synthesis, dalbavancin is bactericidal. Particularly when plasma concentrations are taken into account, dalbavancin is more consistently bactericidal than vancomycin and teicoplanin. Like other glycopeptides, in vitro killing by dalbavancin is best described as time-dependent, suggesting the potential importance of T>MIC as a PD parameter.

Most minimum bactericidal concentration (MBC) and time-kill studies have been directed at staphylococci, including MRSA and VISA isolates. Against virtually all isolates tested,

whether in the presence or absence of 50% human serum, dalbavancin MBCs, or concentrations producing at least a 3 $\log_{10}$ reduction in titer in time-kill experiments, were below levels maintained in human plasma throughout the dosing interval with the proposed regimen (Goldstein 2007). Studies in which precautions have been taken to ensure solubility and to prevent dalbavancin from adhering to plastic surfaces demonstrated dalbavancin MBC values to be close to the MIC values for most staphylococcal and streptococcal isolates tested. A typical kill curve is presented in Figure 11.

Figure 11 Bactericidal Activity of Dalbavancin Against a MRSA Strain



Abbreviations: MRSA = methicillin-resistant *Staphylococcus aureus*; CFU = colony-forming units

4.1.1.3 In Vivo Efficacy in Animal Models of Infection

The efficacy of dalbavancin was examined in a number of animal infection models in immunocompetent mice, rats and rabbits and in immunocompromised mice and rats. The models included severe localized and systemic infections, such as granuloma pouch, endocarditis and lobar pneumonia. Endpoints included survival and bacterial burden in different tissues. Consistent with its in vitro antibacterial potency and PK, in all of these studies, dalbavancin was active at lower and/or less frequent doses than the antimicrobial agents used as comparators.

Efficacy against *S. aureus* was correlated with drug exposure in experiments in rats and rabbits simulating SSSIs. In a granuloma pouch model in rats, the kinetics of MRSA growth and killing were correlated with the drug concentrations in situ. A single 10 mg/kg dose of dalbavancin reduced the bacterial load and suppressed regrowth over a period of several days. In order to achieve similar activity, vancomycin was administered as 4 doses of 100 mg/kg at 12-hour intervals. In a foreign body infection model in rabbits, the rate of device colonization by a *S. aureus* strain was lower in dalbavancin-treated animals than in vancomycin-treated animals.

4.1.1.4 Potential for Antagonism or Synergism

At concentrations up to the mean peak plasma concentration achieved in humans with the proposed dosage, dalbavancin did not antagonize the in vitro activity of antibiotics active

against Gram-negative or other Gram-positive bacteria. Potentially useful synergy was observed between dalbavancin and oxacillin against some MRSA and VISA strains.

4.1.1.5 Studies in Selection for Resistance

High-level glycopeptide resistance, affecting both vancomycin and teicoplanin, requires the presence and expression of the *vanA* gene cluster, consisting of several genes needed to substitute the altered cell wall precursor depsipeptide D-ala-D-lac for the normal peptide D-ala-D-ala as well as regulatory genes that respond to both glycopeptides. Multi-genic resistance of this type cannot simply be selected by exposure to glycopeptides, but requires the presence of another organism that already possesses these determinants and can transfer them. Six staphylococcal isolates (3 strains of MRSA, 1 VISA strain, 1 MSSA, and 1 methicillin-resistant *Staphylococcus epidermidis* [MRSE]) were passaged in dalbavancin, with vancomycin used as the comparator (Goldstein 2007). Variants with increased dalbavancin MIC were not obtained with any strain. Direct selection experiments on agar using large inocula also failed to detect resistant variants.

Emergence of resistance has not been observed in animal infection studies or in clinical trials (Section 7). By maintaining bactericidal concentrations of dalbavancin throughout the treatment period, it is not expected that resistance in infecting organisms would emerge during treatment.

4.1.1.6 Potential for Cross-resistance to Other Antibacterial Agents

The potency of dalbavancin was not affected by resistance of isolates to other classes of antibacterial agents.

4.1.1.7 In Vitro Data from Isolates in Phase 3 Clinical Trials

Microbiological data were obtained for isolates from 3 phase 3 double-blind, double-dummy, multicenter comparative studies of the efficacy of dalbavancin in the treatment of ABSSSI (DUR001-301, DUR001 302), and a subset of patients from cSSSI study VER001-9 that met the criteria for ABSSSI. The bacterial pathogens isolated from clinical trial subjects were consistent with the epidemiology of the disease under study, and the in vitro activity of dalbavancin against the isolates was within expected MIC ranges, as observed in surveillance studies (Section 7.4.1.1).

The proposed human dosage regimen of 1000 mg IV on Day 1, followed by 500 mg IV on Day 8 was efficacious in eradicating organisms from the sites of infection and no emergence of resistance to dalbavancin was observed in any study.

4.1.1.8 Proposed Susceptibility Breakpoint

The proposed susceptibility interpretive criterion for dalbavancin is ≤ 0.25 µg/mL, determined by broth microdilution according to CLSI (CLSI 2012a, CLSI 2013). At present, as there is no clear signal as to what constitutes resistance, it is suggested that isolates with MIC > 0.25 µg/mL be considered non-susceptible. The primary considerations include wild-type MIC distribution, bactericidal activity of concentrations of unbound dalbavancin that are present in human serum throughout the treatment period with the proposed dosage regimen,

efficacy in clinical trials, and PK/PD modeling based on human clinical data and animal infection model studies. This is discussed further in Section 7.5 of this briefing document.

4.1.2 Secondary Pharmacodynamics Studies

The target of dalbavancin's mechanism of action is bacteria-specific, and is not expected to significantly interfere with other physiologic processes. In addition, dalbavancin does not interfere with any CYP450 isoenzyme system, and as such, is not expected to interfere with the pharmacological mechanisms of most agents expected to be administered concurrently in the community or hospital setting (Section 4.2.3).

Dalbavancin was studied in secondary pharmacodynamics studies in vitro to evaluate its potential effect on the cardiovascular (hERG, Purkinje fibers) system, coagulation (platelet aggregation) and other physiologic targets, as noted below (Sections 4.1.2.1, 4.1.2.2 and 4.1.2.3).

4.1.2.1 Potential Effects on the Human Ether-à-go-go Related Gene (hERG) System

Dalbavancin did not inhibit the hERG channel current in vitro, and had no effect on the action potential duration (APD) in rabbit Purkinje fibers at concentrations similar to projected blood levels at therapeutic doses. The absence of effects in vitro was confirmed in cardiovascular safety pharmacology studies in vivo (Section 4.1.3.1), as well as the absence of an effect on QT/QTc prolongation in nonclinical as well as human studies (Section 5.2.2 and Section 8, respectively), where it was demonstrated that a therapeutic (1000 mg) and supratherapeutic (1500 mg) dose of dalbavancin did not prolong QT/QTc in healthy volunteers.

4.1.2.2 Potential Effects on Coagulation

In an in vitro study using rabbit platelets, concentrations of dalbavancin approximately 7 times the projected human C_{max} inhibited collagen-induced platelet aggregation. This effect was not considered clinically relevant in view of the absence of an effect on bleeding time in rats in vivo at doses approximating the exposure in humans at the proposed therapeutic dose (Section 4.1.3.4). In addition, no evidence of a clinically relevant effect on platelets at projected human exposures was observed in toxicology studies (Section 4.3) or in clinical trials (Section 8).

4.1.2.3 In Vitro Studies of Potential Effects on Other Physiologic Targets

Dalbavancin was evaluated for potential interaction against a broad panel of 120 in vitro targets, including receptors, ion channels, uptake sites, and enzymes. In this assortment of tests, dalbavancin displayed limited affinity for most physiologic targets tested at high concentration compared to projected blood concentrations observed at human therapeutic doses. Rapid decline in plasma concentration of dalbavancin by approximately 75% by 48 hours following injection suggest that the effect of binding would be significantly reduced after a brief period following dosing. Based on the results of nonclinical toxicology studies (Section 4.3) and clinical adverse event reports (Section 8), it is not expected that the results of the in vitro assays would translate to biologically significant effects in animals or patients.

Further, these results do not indicate a likely interaction with other therapeutic targets or a potential for clinically relevant PD interactions.

4.1.3 Safety Pharmacology Studies

The cardiovascular, respiratory, and central and autonomic nervous system safety pharmacology of dalbavancin was evaluated according to ICH S7A guidelines at doses at or above the human dose. These studies were conducted in mice, rats, dogs, and in tissues from rabbits.

4.1.3.1 Potential Effects on the Cardiovascular System

The in vivo effects of dalbavancin on the cardiovascular system in vivo were evaluated in studies in anesthetized and conscious telemetered dogs.

A rapid, 30 second IV infusion of 10 mg/kg of dalbavancin in anesthetized dogs produced a 50% decrease in blood pressure, which was reversed by administration of noradrenaline. The observed hypotensive effect is attributed to the rapid infusion at a peak plasma concentration that would exceed that of the human C_{max} observed in clinical studies. When dalbavancin was given as a 15-minute or longer infusion, blood pressure or other hemodynamic parameters were not affectd. Where blood pressure decreases due to rapid infusions were observed, there was also an increase in the incidence of associated clinical signs (cutaneous erythema and swelling). Blood pressure and heart rate effects were, like cutaneous erythema and swelling, attributed to histamine release (Wold 1981; Masini 1985).

In studies conducted in conscious telemetered dogs, doses up to 60 mg/kg dalbavancin (approximately 3-4 times the cumulative human dose on a weight basis) produced no abnormal electrocardiograph arrhythmias, conduction disturbances, or quantitative abnormalities (including QT or QTc interval prolongation). Some decreases in mean arterial blood pressure and increases in heart rate that were observed in these studies were not considered to be clinically relevant. These hemodynamic effects were accompanied by clinical signs of cutaneous swelling and/or erythema, particularly of the face and paws. As with the above studies in anesthetised dogs, these effects were attributed to histamine release.

4.1.3.2 Potential Effects on the Respiratory System

Dalbavancin doses of approximately 1.4 times the initial human dose on a weight basis had no effect on respiration in conscious rats.

4.1.3.3 Potential Effects on the Central and Autonomic Nervous Systems

In central nervous system (CNS) and autonomic nervous system (ANS) studies in instrumented conscious rats, no statistically significant effect on any parameter were observed.

4.1.3.4 Potential Effects on Bleeding Time

Dalbavancin did not have an effect on coagulation in vitro (Section 4.1.2.2). In Wistar male rats, no statistically significant effect was observed on bleeding time.

4.1.3.5 Clinical Implications of Nonclinical Safety Pharmacology Findings

On the basis of the safety pharmacology evaluations conducted in mice, rats and dogs, no significant AEs were observed for dalbavancin doses up to approximately the cumulative human dose, or 1.4 times the initial 1000 mg human dose, on a weight basis, the only observed effect with potential clinical relevance was a non-dose-dependent decline in blood pressure (with a small correlating increase in heart rate), that intermittently occurred during or immediately after infusion of dalbavancin doses ≥ 30 mg/kg in dogs. These hemodynamic changes were associated with skin swelling and erythema and were attributed to histamine release. Similar hemodynamic effects have been reported rarely in human clinical trials of dalbavancin, with changes in vital signs in patients were generally mild, transient and similar between dalbavancin and comparators. A single case of bronchospasm/anaphylactoid reaction reported in a phase 3 trial was considered possibly related to study drug (Section 8.4.5).

In clinical pharmacology trials in healthy volunteers, neither a therapeutic (1000 mg) and supratherapeutic (1500 mg) dose of dalbavancin produced a significant effect on cardiac repolarization (Section 5.2.2).

4.2 Nonclinical Pharmacokinetics

4.2.1 Absorption

PK data were collected in studies using mice, rats (adult and juvenile), rabbits, dogs, and minipigs. Dalbavancin administered intravenously exhibited dose-proportional PK similar to humans in rats and dogs, the two species selected for the majority of nonclinical safety studies.

Validated analytical methods used for the measurement of the 5 major homologs in dalbavancin (Section 3.1) and its metabolites in plasma, urine, and feces of animals given radiolabeled drug demonstrated that virtually all the drug-derived radioactivity in plasma is intact drug, with minor amounts of 2 metabolites isolated in the urine and feces of rats, dogs and humans (Section 4.2.3 and Section 4.2.4).

4.2.2 Distribution

Dalbavancin is widely distributed throughout the body into all organs and tissues examined after IV administration. There was no observation of preferential accumulation in skin versus plasma in either rats or minipigs. Dalbavancin kinetics were consistent across species, with plasma clearance (CL) scaled allometrically by species body weight. Dalbavancin crossed the rat placenta and was found in fetal rat plasma.

4.2.3 Metabolism

Dalbavancin does not interfere with hepatic CYP450 isoenzymes. The drug is not metabolized in vitro by rat, dog, or human hepatic microsomes, nor by rat, dog, or human hepatocytes; or human kidney microsomes. Dalbavancin did not affect the metabolism of marker substrates by isolated human hepatic microsomes. Administration of dalbavancin to rats did not induce any CYP450 activity.

Similar dalbavancin metabolite profiles are observed across species. Two metabolites of dalbavancin: OH-dalbavancin and MAG have been observed in the urine of rats, dogs, and humans (Secton 4.2.4 and Section 5.2.1.3). Both metabolites are either undetectable or close to the limit of detection in human plasma, have less potent antibacterial activity than dalbavancin (MAG: 2-32x higher MIC; OH-dalbavancin: 2-64x higher MIC), and contribute little, if anything to its in vivo activity.

4.2.4 Excretion

Dalbavancin has dual routes of excretion (urinary and fecal) and is excreted as intact drug and metabolites. Dalbavancin is excreted in the urine and feces of rats, dogs, and humans. Most of the dose is excreted as intact drug in the urine. The 2 metabolites, hydroxy dalbavancin and MAG (Section 4.2.3) are found in the urine, as well as with intact drug in animal feces. Human feces contained antimicrobially-active dalbavancin components. Dalbavancin is also excreted into rat milk.

4.3 Toxicology

4.3.1 Toxicology Overview

Nonclinical in vitro and in vivo toxicology studies to support the clinical investigation and registration of dalbavancin were conducted in rats, dogs, and rabbits. The similarity of the PK characteristics of dalbavancin across species supports the use of rats and dogs for safety assessment. Most nonclinical toxicology studies in vivo utilized dalbavancin administered intravenously – the intended route of administration in clinical use. Because PK differences exist between animals and humans, daily dosing was performed in test animals for the duration of the treatment period to conservatively evaluate toxicity during repeated exposure.

Local injection site reactions were commonly observed in the test species. The kidney and liver were identified as target organs in toxicology studies, primarily at drug exposures exceeding those projected in humans at therapeutic dose levels. For the purpose of estimating animal to human exposure ratios, the animal systemic exposure, area under the plasma concentration-time curve (AUC) was estimated as the cumulative exposure for the entire dosing period for subchronic dosing (28 or 90 days), whereas the human exposure for the 2-dose regimen given weekly was estimated as the AUC over a 14-day dosing period.

4.3.2 Local Injection Site-Associated Reactions

Dalbavancin became dose-limiting in subchronic studies, frequently appearing as red or purple discoloration or dark, necrotic lesions in the tail, leading to early termination. Clinical signs other than injection site changes attributed to extravasation were generally observed at elevated doses (eg, $\geq$ 40 mg/kg/day).

4.3.3 Infusion-Associated Reactions

Infusion reactions similar to those described in the safety pharmacology studies (Section 4.1.3.1) were observed in all toxicology studies in dogs where the infusion period was $\leq$11 minutes and in all cardiovascular safety pharmacology studies in dogs where the infused dose was $\geq$ 30 mg/kg (Section 4.1.3.1). A single study in dogs with a dose of

10 mg/kg/day, administered at a concentration of 10 mg/mL over 30 minutes, was negative for infusion reactions, suggesting that these effects were related to a combination of the size of the administered dose, and/or dose solution concentration, and the rate of infusion. Doses that exceeded the maximum tolerated dose (MTD) in this species were associated with renal and/or hepatic target organ toxicity leading to morbidity and mortality.

4.3.4 Systemic Effects

Adverse effects of dalbavancin consisted of 2 components: (1) clinical and histopathology findings suggestive of toxicity to the kidney and liver; and (2) cytoplasmic vacuolation and/or pigment accumulation in multiple organs that was not considered toxicologically meaningful.

4.3.4.1 Target Organ Effects

The principal target organs in toxicology studies were the kidney and liver. Renal and hepatic effects were dose-dependent and occurred in both rats and dogs. Effects in these organs included macroscopic, organ weight, clinical chemistry, and/or histopathology changes. Morbidity related to hepatic and renal toxicity observed at a high dose (40 mg/kg/day) in male dogs required either euthanasia in some dogs or suspension of dosing in others. Local and systemic toxicologic changes were partially reversible following cessation or reduction of dosing. The no observed adverse effect levels (NOAELs) for both rats and dogs were 10 mg/kg/day after 28 days, and 5 mg/kg/day after 90 days of daily dosing.

4.3.4.2 Vacuoles and Pigmentation

Vacuoles and/or dark pigment were observed in the cytoplasm of macrophages and other cells in a variety of tissues (including hepatocytes and renal tubular epithelium in rats and dogs and mammary gland and pancreatic acinar epithelium in rats). Vacuolated macrophages with or without intracytoplasmic dark pigment were observed at the injection site and in lymph nodes, spleen, thymus, liver, and adrenal. The pigment did not stain positively for iron. The combination of vacuolation and pigmentation suggests that the pigment could be lipofuscin, ie, “wear and tear” pigment associated with increased turnover of lipid-rich cell membranes and is not considered evidence of toxicity.

4.3.4.3 Genotoxicity Studies

Dalbavancin was not observed to be genotoxic, having been evaluated in a series of genotoxicity assays that included in vitro mammalian cell assays for gene mutation (induction of mutations at the hypoxanthine-guanine phosphoribosyltransferase [HGPRT] locus in V79 Chinese hamster lung [CHL] cells) and cytogenetic evaluation of chromosomal damage in Chinese hamster ovary (CHO) cells, plus an in vivo mouse micronucleus assay. All assays met the criteria for validity and all were negative.

4.3.4.4 Reproductive Toxicology Studies

Dalbavancin was not teratogenic in rats or rabbits at maternally toxic doses. In rats, the no observed effect levels (NOELs) for mating and fertility and embryo fetal development were 15 mg/kg/day, or approximately equal to the human dose on an exposure basis. The NOEL

for viability and growth of offspring in a peri- and post-natal evaluation was 30 mg/kg/day. Reduced fertility, an increased incidence of embryolethality, reductions in fetal weight, skeletal ossification and increased neonatal mortality were observed at 45 mg/kg/day (approximately 3.5 times the human exposure) in rats. In rabbits, abortion occurred in conjunction with maternal toxicity.

4.3.4.5 Toxicology Studies in Juvenile Animals

Two dalbavancin toxicology studies conducted in juvenile rats at dose levels of 10, 20 and 40 mg/kg/day for up to 56 days (post-natal days 7 through 63) were consistent with those previously observed in adult rats at the same dose levels.

4.3.4.6 Conclusions from Nonclinical Safety Studies

The toxicologic effects of dalbavancin at clinically relevant doses appear to reflect its local irritancy and slow systemic elimination. Target organs of toxicity were the kidney and liver at exposures significantly higher than those expected from human therapeutic dose levels. Effects at doses and/or durations comparable to the intended clinical regimen were not considered adverse, with the exception of the occurrence of abortions in rabbits (but not rats).

The toxicity profile supports the proposed clinical use for serious infections of the skin and surrounding soft tissues.

5 CLINICAL PHARMACOLOGY

5.1 Introduction

Dalbavancin displays a PK profile which allows once weekly IV dosing, affording 14 days of antibiotic coverage with 2 weekly doses (Section 4.2). The efficacy and safety of IV dalbavancin for treatment of serious bacterial infections caused by Gram-positive pathogens, in particular those caused by staphylococci and streptococci, have been confirmed in phase 2 and phase 3 clinical trials (Section 6, Section 7 and Section 8) and consititute the clinical support for this application.

Dalbavancin possesses a long β half-life ($t_{1/2}$) of 8.5 days, with a terminal half-life ($T_{1/2}$) of over 14 days, thereby allowing for the proposed once-weekly dosing. The recommended adult clinical dose regimen for dalbavancin for the treatment of ABSSSI is 2 single doses, given 7 days apart: 1000 mg on Day 1 and 500 mg on Day 8. For patients with chronic renal impairment (creatinine clearance [CL_{CR})] < 30 mL/min) and not receiving regular renal dialysis, the recommended dose regimen is reduced by 25%, to 750 mg on Day 1 and 375 mg on Day 8.

The highest single dose of dalbavancin administered to healthy subjects was 1500 mg. The highest dosage studied over a 7-day period was a daily dosage regimen with a cumulative dosage of 1600 mg. The highest cumulative dosage administered to healthy subjects was 4500 mg, administered as an initial 1000 mg dose, followed weekly by 500 mg for up to 7 additional weeks. Across the entire phase 1 clinical program, the incidence of any one type of adverse event was low.

5.2 Human Pharmacokinetics

The PK of IV dalbavancin have been studied in healthy subjects, special populations, and the intended patient population. PK observations have been a part of each clinical pharmacology study and across several patient studies via population PK, and are summarized in this section.

The PK of dalbavancin were evaluated in 17 clinical studies:

- 9 healthy-volunteer studies, including 1 pilot single-dose study of 1500 mg dalbavancin, 1 multiple dose study evaluating 1000 mg on Day 1 and 500 mg weekly for 4 to 8 weeks, 2 ascending dose studies with single- and multiple-dose regimens, 2 excretion and distribution studies, 1 study examining the effect of dalbavancin on intestinal flora, 1 thorough QT study, and 1 study in healthy Japanese subjects. A total of 219 healthy volunteers were administered dalbavancin in these studies
- 4 studies in subjects with hepatic impairment, renal impairment, or subjects undergoing hemodialysis. A total of 74 subjects were administered dalbavancin in these studies
- 3 patient studies, with data from a total of 532 patients that were combined and evaluated in a population PK analysis. Included in the analysis were 502 patients with SSSI

- 1 study in pediatric subjects with resolving infections, which enrolled 10 subjects aged 12 to 16 years

A summary of the PK of dalbavancin is highlighted below:

- The inter-individual variability observed for dalbavancin plasma concentrations and PK parameters is very low.
- The disposition of dalbavancin is triphasic.
- The predominant elimination rate was characterized by a β half-life ($t_{1/2}$) of 8.5 days.
- Drug exposure, as measured by C_{max} and by AUC, increased in a proportional manner with increasing dosage. The estimated C_{max} following a 1000 mg IV dose is ~250 µg/mL; the mean AUC for the proposed 2-dose regimen is ~26,000 µg•h/mL.
- Dalbavancin showed good penetration into the extracellular fluid in skin tissue.
- Estimates of dalbavancin total clearance (CL) were consistent across studies and did not vary with dose.
- Dalbavancin is not a substrate, inducer, or inhibitor of hepatic CYP450 isoenzymes.
- Dalbavancin has a low potential to produce, or be the subject of, drug-drug interactions.
- Dalbavancin is eliminated by both renal and non-renal pathways.
  - Dosage adjustment is not required for mild to moderate renal impairment or subjects with severe renal impairment receiving regularly-scheduled dialysis. Based on the PK parameters and simulations, a dosage adjustment (25% dose reduction) is recommended for patients with severe renal impairment who do not receive regular dialysis.
  - No dosage adjustment of dalbavancin is required for patients with any degree of hepatic impairment.
  - No dosage adjustment is required based on body mass index (BMI) or body weight.
- Monte Carlo analysis supports a susceptibility breakpoint of 2 mg/L or higher for streptococci and a susceptibility breakpoint of 1 mg/L for *S. aureus*. However, a conservative susceptibility breakpoint of ≤0.25 mg/L is proposed for both staphylococci and streptococci based upon clinical response data and surveillance studies (Section 7).

5.2.1 Basic Pharmacokinetic Properties of Dalbavancin

5.2.1.1 Absorption

PK parameters following a single 1000 mg IV dose of dalbavancin are summarized in Table 19. The mean concentration-time profiles after administration of a single 1000 mg dose of dalbavancin are provided in Figure 12.

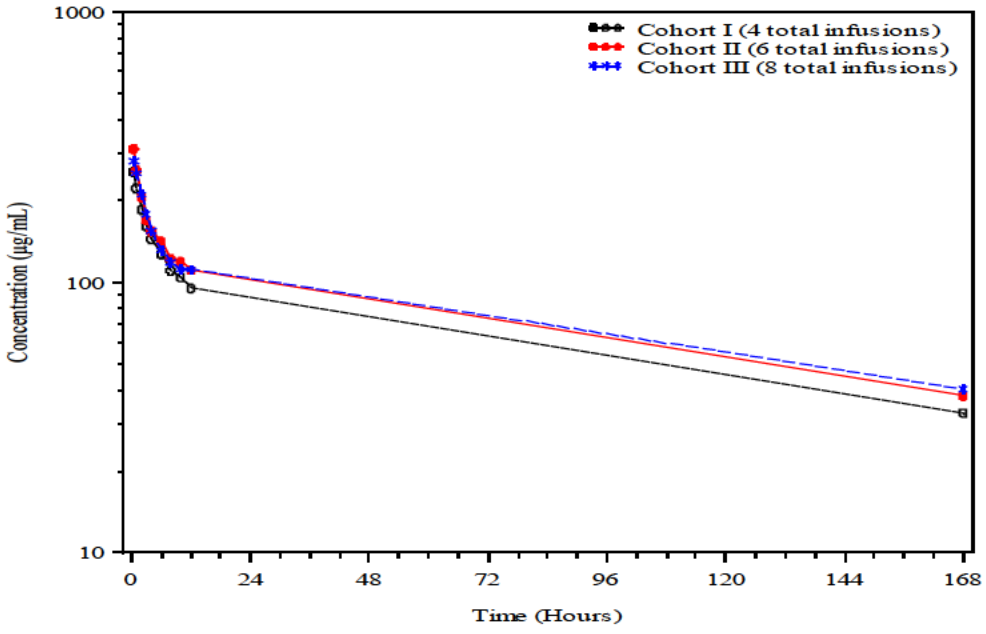
Table 19 Mean (%CV) Dalbavancin Pharmacokinetic Parameters in Healthy Subjects

Parameter	Single 1000 mg Dose Administered as IV infusion
C_{max} (mg/L)	287 (13.9)[a]
AUC_{0-24} (mg•h/L)	3185 (12.8)[a]
AUC_{0-Day7} (mg•h/L)	11160 (41.1)[b]
$AUC_{0-\infty}$ (mg•h/L)	23443 (40.9)[b]
Terminal $T_{½}$ (h)	346 (16.5)[b,c]
V_{ss} (L)	13.8 (16.5)[e]
CL (L/h)	0.0513 (46.8)[b]

[a] Subjects from DUR001-102 who received 1000 mg IV single dose (n=50)
[b] Subjects from VER001-15 who received 1000 mg IV single dose (n=12)
[c] This value corresponds with the $t_{½}$. Based upon population PK analyses of data from patients, the effective β half-life ($t_{1/2}$) is approximately 8.5 days (204 hours)
[d] Subjects from VER001-19 who received 1000 IV single dose (n=9)

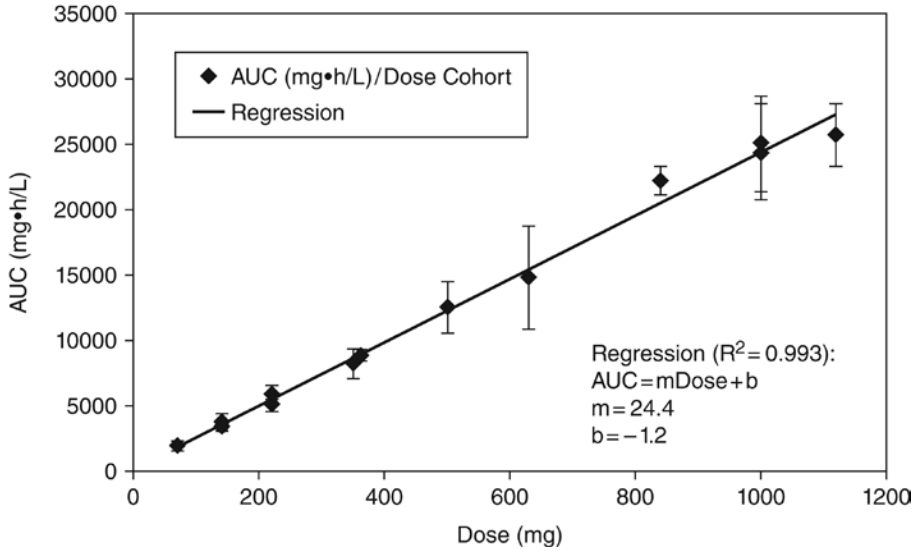
Abbreviations: AUC_{0-24} = area under the curve from 0 to 24 hours; AUC_{0-Day7} = area under the curve from 0 to Day 7; $AUC_{0-\infty}$ = area under the curve from 0 to infinity ;CL = clearance; C_{max} = maximum plasma drug concentration after first dose; %CV = coefficient of variation; IV = intravenous; PK = pharmacokinetics; $t_{1/2}$ = terminal elimination half-life

Figure 12 Mean Plasma Concentrations over Time for Dalbavancin After Administration of a Single 1000 mg Dose



Drug exposure, as measured by AUC, increased in a proportional manner with increasing dosage, as shown in Figure 13. Systemic exposure following escalating single doses of dalbavancin were examined and the PK parameters were consistent across studies.

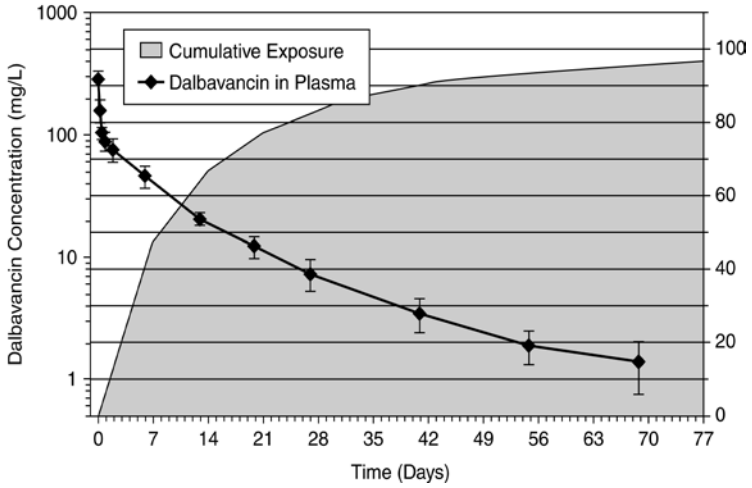
Figure 13 Dalbavancin Exposure Versus Dose



Abbreviations: AUC = area under the curve

Following 1000 mg dalbavancin, AUC was approximately 25,000 mg•h/L. Almost 50% and 70% of the exposure is observed through the first and second weeks postdose, respectively. Approximately 90% of drug exposure is observed through 5 weeks postdose (Figure 14). The mean estimates of $t_{1/2}$ vary somewhat across studies due to differences in PK sampling durations.

Figure 14 Dalbavancin Plasma Concentration-Time Profile Following 1000 mg Dalbavancin and Cumulative Exposure over Time



Dalbavancin's PK properties following the recommended therapeutic regimen of weekly dosing for 2 weeks, followed by additional weekly doses of 500 mg (Study DUR001-104) for a total regimen of up to 8 weeks are summarized in Table 20.

Table 20 Mean (SD) Pharmacokinetic Data From Multiple Doses of Dalbavancin Administered to Healthy Subjects[a]

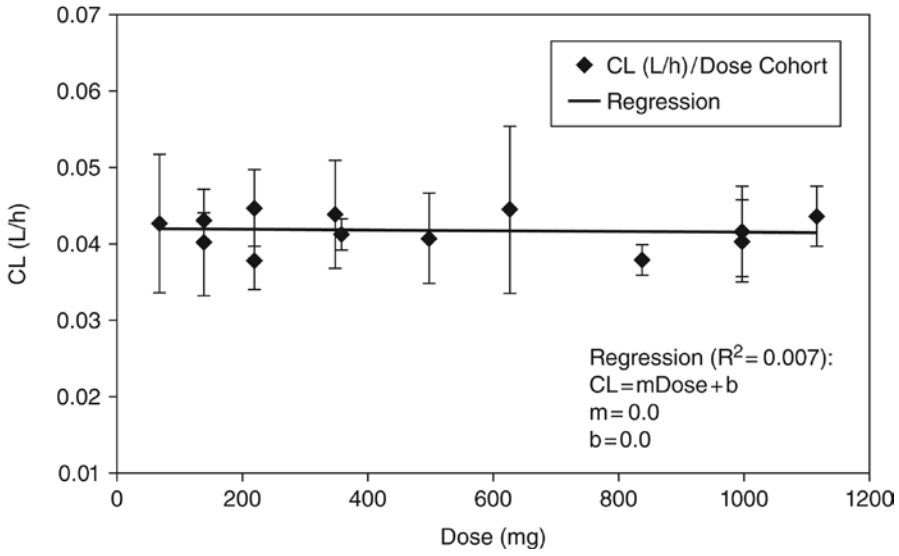
Study (Day) Dose (mg)	Cmax (mg/L)	AUC0-t (mg•h/L)	t½ (h)	CL (L/h)
Day 22 1000/500	160 (22.4)	10203 (1522)	98.9 (9.99)	NC
Day 36 1000/500	187 (24.4)	12993 (2308)	98.9 (9.60)	NC
Day 50 1000/500	180 (19.8)	12173 (2154)	109 (15.9)	NC

[a] Subjects received 1000 mg on Day 1 followed by 500 mg once weekly for 3, 5, or 7 weeks. PK parameters were calculated after the last 500 mg dose received. End time for AUC calculation was 168 hours. $T_{1/2}$ was calculated using concentrations collected on Day 1 (ie,ie, out to 12 h) and is therefore not comparable to $t_{1/2}$ estimates from other studies. Clearance was not calculated in this study but the mean value (calculated as 500 mg/AUC_{0-t}) would be consistent with previous multiple dose studies (0.04-0.05 L/h).

Abbreviations: AUC_{0-t} = area under the standard curve from 0 to time t; CL = clearance; C_{max} = maximum plasma drug concentration after first dose; NC= not calculated; SD = standard deviation; $t_{1/2}$ = terminal elimination half-life

Estimates of dalbavancin total CL were consistent across studies and did not vary with dose (Figure 15). Mean CL was estimated as 0.04 L/h. The variability of the PK parameters, both across and within studies and dose cohorts, was low, with a coefficient of variation (%CV) of < 21% for all plasma PK parameters in 2 studies following a 1000 mg IV dose.

Figure 15 Dalbavancin Clearance Versus Dose



Abbreviations: CL = clearance

In several multiple-dose studies, dalbavancin was found to have dose-proportional PK, low inter-individual variability, and a predominant $t_{1/2}$ of approximately 8 days. Clearance was consistent and approximately 0.05 L/h across all dosage cohorts; no relationship was

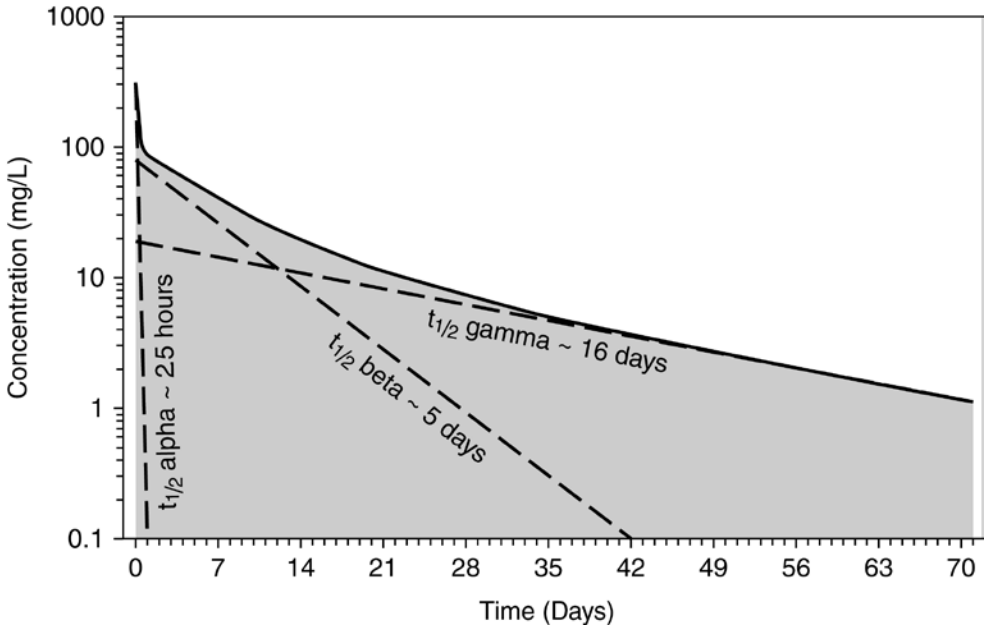
observed between PK and gender. The design of Study DUR001-104, with weekly dosing for up to 8 weeks, more accurately reflects the intended clinical dosage regimen of 1000 mg on Day 1 and 500 mg on Day 8. The results of this study suggest that there is no accumulation in dalbavancin concentrations when employing this type of weekly regimen and that the PK of dalbavancin does not appear to change substantially with time.

5.2.1.2 Distribution

In the largest single-dose cohort studied (VER001-19; n=9), dalbavancin was shown to distribute into a steady-state volume of distribution (V_{SS}) of 14 L. This is a distribution volume that is approximately 20% of body weight, and consistent with the assumption that the drug is distributed in the extracellular fluid. When adjusted by body weight, the V_{SS} observed for humans (~0.2 L/kg) was similar to other species studied (mice, rats, rabbits, dogs, and minipigs). Animal studies showed that dalbavancin was well distributed throughout the body (Section 4.2.2).

The disposition of dalbavancin is triphasic. The deconvolved areas representing each of different disposition phases is shown in Figure 16. The dalbavancin plasma concentration-time profile is from Study VER001-19, which provided the best estimate of dalbavancin disposition, sampling the concentration-time profile through 10 weeks. The initial distributive phase (alpha phase) is short and can be characterized by a $t_{1/2}$ of approximately 2.5 hours. An elimination phase (beta phase) follows that accounts for the majority of drug elimination ($t_{1/2}$ approximately 5 days). This elimination phase has been estimated with a $t_{1/2}$ as long as a week in some studies. In patients, the predominant elimination rate was characterized by a $t_{1/2}$ of 8.5 days. With an adequately long study, sensitive assay, and extensive sampling, a terminal elimination phase can be observed with a $T_{1/2}$ of 16 days. The terminal elimination phase characterizes the lower concentrations (< 10 mg/L) at later times in the concentration-time curve (> 28 days).

Figure 16 Plasma Concentration-Time Profile Following 1000 mg Dalbavancin

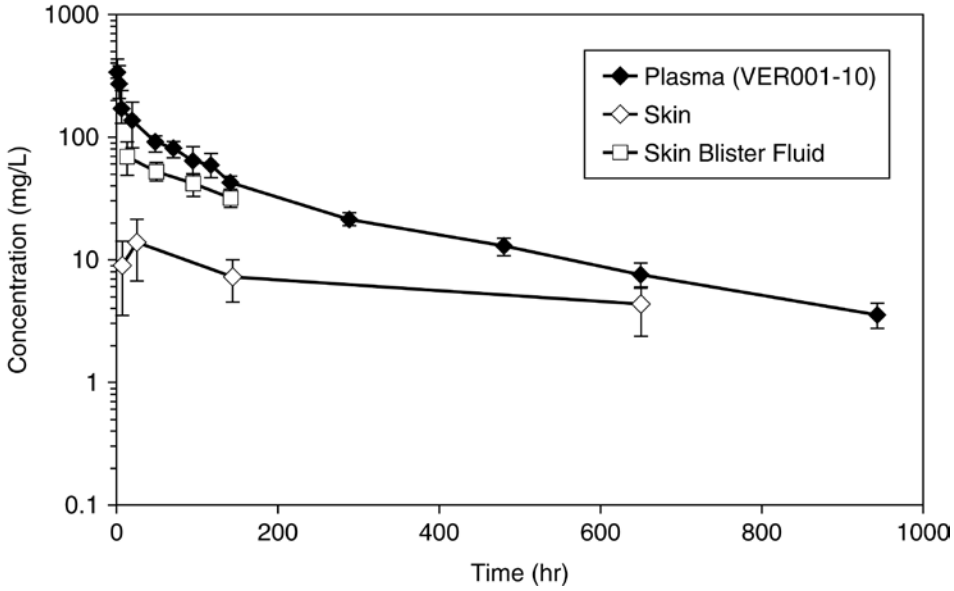


Abbreviation: $t_{1/2}$ = terminal elimination half life

SKIN PENETRATION

Dalbavancin showed good penetration into the extracellular fluid in skin tissue. Concentrations of dalbavancin in skin and skin blister fluid following administration of 1000 mg IV were examined in Clinical Studies VER001-10 and VER001-19, respectively. The mean concentration versus time profile for dalbavancin in plasma, skin, and skin blister fluid are compared in Figure 17. Concentrations for dalbavancin in skin were above 7 mg/L through Day 7 and remained above 4 mg/L through Day 28. Concentrations for dalbavancin in skin blister fluid were higher than those of skin, reflecting the higher concentration in extracellular fluid, and were above 30 mg/L through Day 7. The relative exposure of dalbavancin in skin blister fluid was determined by comparing the exposure in blister fluid to that in plasma through Day 7 postdose. Dalbavancin showed good penetration with a relative exposure of 60%.

Figure 17 Dalbavancin Pharmacokinetic Profiles in Plasma, Skin, and Skin Blister Fluid Following Single 1000 mg Dose of Dalbavancin



PROTEIN BINDING

The plasma protein binding of dalbavancin is approximately 93%, and is consistent across the wide therapeutic range studied, as well as subjects with varying degrees of hepatic or renal impairment. Dalbavancin protein binding was similar in human and animal studies (Sections 1.5.7 and 4.3.1). Based upon an algorithm for determining clinical significance of potential protein binding displacement interactions put forth by Rolan (1994), dalbavancin is unlikely to be susceptible to clinically significant protein binding displacement interactions due to its wide therapeutic index and low hepatic extraction ratio.

PENETRATION INTO THE CENTRAL NERVOUS SYSTEM

No drug penetration into cerebral spinal fluid (CSF) was observed in a limited sampling of CSF of 2 patients with CRBSI (Study VER001-4).

PREGNANCY AND LACTATION

Dalbavancin has not been studied in pregnant or nursing women. However, the drug crosses the rat placenta and can be found in fetal blood. Dalbavancin is also excreted in rat milk.

5.2.1.3 Metabolism

Dalbavancin is not a substrate, inducer, or inhibitor of hepatic CYP450 isoenzymes. Incubation of dalbavancin with rat, dog, or human hepatic microsomes or hepatocytes did not result in appreciable loss of parent compound. Dalbavancin did not inhibit the activity of CYP1A2, 2A6, 2B6, 2C19, 2C9, 2D6, 2E1, or 3A4. A rat study performed to evaluate the potential of dalbavancin to induce hepatic microsomal enzymes found no clinically relevant changes in any P450 isoenzyme. Microsomes from dalbavancin-treated rats did not

metabolize the drug. No biotransformation was observed when dalbavancin was incubated with human kidney microsomes.

Dalbavancin is metabolized to a small extent to form 2 minor metabolites in all species studied (Section 4.2.3). No significant amounts of these metabolites have been observed in human plasma; however, a minor dalbavancin metabolite, OH-dalbavancin, has been observed in human urine. Metabolic transformation is due to hydroxylation in the omega-3 position of the C-11 branched side chain (fatty acid side chain) of the most abundant dalbavancin homolog, B_0. A second metabolic transformation results from removal of the acyl sugar moety to form MAG.

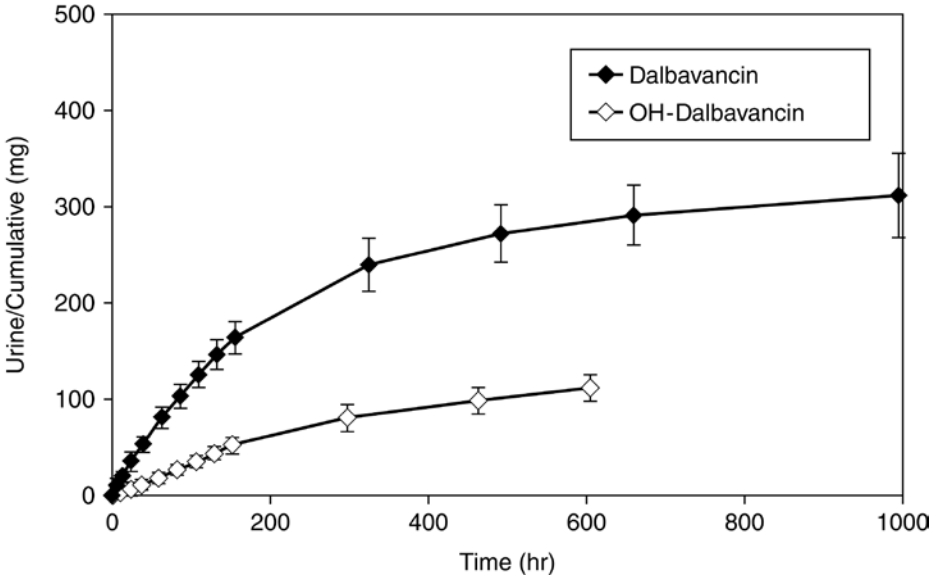
A total of 8% to 12% of the administered dose is excreted as OH-dalbavancin in human urine, with somewhat greater levels observed in the urine in rat and dog studies (~10% and 23% of the administered dose, respectively (Section 4.2.3). The presence of this minor metabolite is clinically insignificant because of the low levels of OH-dalbavancin observed in plasma and because OH-dalbavancin is significantly less active than dalbavancin (MIC = 2-64x higher). Following 1000 mg dalbavancin, concentrations of OH-dalbavancin in human plasma were below the limits of quantitation (< 0.4 mg/L).

Small amounts of MAG were also observed in urine following administration of dalbavancin. MAG is present as a manufacturing-related compound in the drug product, but may also be produced in vivo by biotransformation or degradation. MAG had a faster clearance into urine than dalbavancin, with greater relative amounts excreted over the first few days post-dose. Like OH-dalbavancin, levels of MAG in plasma were either very low or undetectable. MAG is also less active than dalbavancin (MIC = 2-32x higher) and the presence of MAG is therefore clinically insignificant (Section 4.2.3). MAG has been found in the urine and feces of rats and dogs (≤ 5% of the dose) and those metabolite profiles are consistent with human observations.

5.2.1.4 Excretion

Dalbavancin is excreted as intact drug and OH-dalbavancin in urine, and as intact drug in feces. The estimated fraction of drug excreted unchanged in the urine is 33% of the administered dose. The estimated amount of metabolite excreted in the urine is 12% of the total dose. The cumulative amount of dalbavancin and OH-dalbavancin excreted into urine versus time following a dose of 1000 mg dalbavancin is shown in Figure 18. Renal CL of intact dalbavancin is 0.0138 L/h. These observations show renal excretion to be an important, but not exclusive, elimination pathway. Approximately 20% of drug excreted into feces.

Figure 18 Cumulative Amount of Dalbavancin and OH-Dalbavancin Excreted into Urine Following Single 1000 mg Dose of Dalbavancin



Collectively, approximately 70% of the administered dose has been accounted for in collected excreta. The remaining 30% of the administered dose is also likely to be excreted in urine and feces, but may be eliminated at slower rates in the later points in the profile with concentrations in excreta that fall below the quantifiable limits of the assays. A summary of dalbavancin excretion in humans is presented in Table 21.

Table 21 Mean (SD) Excretion of Dalbavancin Following Single 1000 mg Dose of Dalbavancin Administered to Healthy Subjects

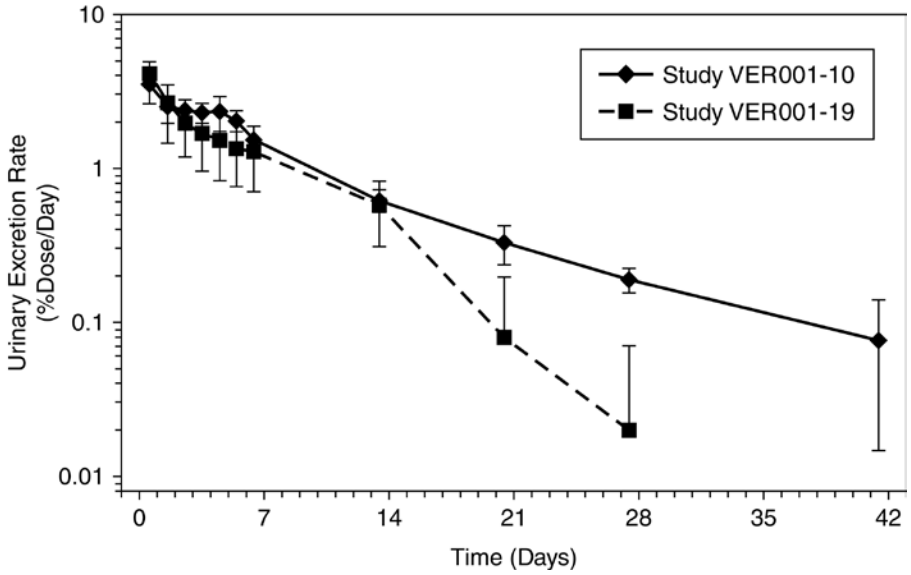
	Urine				Feces	
	Dalbavancin		OH-Dalbavancin		Dalbavancin	
Study	% Dose	CL_{renal} (L/h)	% Dose	CL_{renal} (L/h)	% Dose	CL_{feces} (L/h)
VER001-10	33.0 (3.7)	0.0138 (0.0028)	11.7 (1.9)	0.0049 (0.0008)	NC	NC
VER001-19	19.2 (6.7)	0.0081 (0.0034)	7.8 (1.1)	0.0032 (0.0004)	19.7 (16.0)	0.0080 (0.0065)

Note: VER001-10 had a lower assay limit and better excretion estimate
Abbreviations: CL = clearance; NC = not calculated

Urine was collected and assayed for dalbavancin and OH-dalbavancin in 2 clinical studies, VER001-10 and VER001-19. Dalbavancin urinary excretion rates were similar in both studies, as shown in Figure 19. Approximately 1% to 5 % of the dose is excreted as intact dalbavancin daily during the first week, dropping to > 0.5% of the dose per day through the second week postdose. Differences in the profiles are observed around 21 days postdose, with significantly lower excretion rates observed for subjects in VER001-19. This is an

artifact due to the differences in the levels of quantitation of the assays used in these studies. The assay to measure dalbavancin in urine had a limit of quantitation of 0.5 and 1 mg/L in VER001-10 and VER001-19, respectively. The higher limit of quantitation in VER001-19 did not allow for urine concentrations to be accurately quantitated at the timepoints beyond 2 weeks postdose. The urine excreta profile observed in VER001-10, and subsequent integration of this profile to obtain the amount of dalbavancin excreted in urine produces the best estimate of dalbavancin urinary excretion.

Figure 19 Comparison of Urinary Excretion Rates Observed in Clinical Studies VER001-10 and VER001-19 Following Single 1000 mg Dose of Dalbavancin

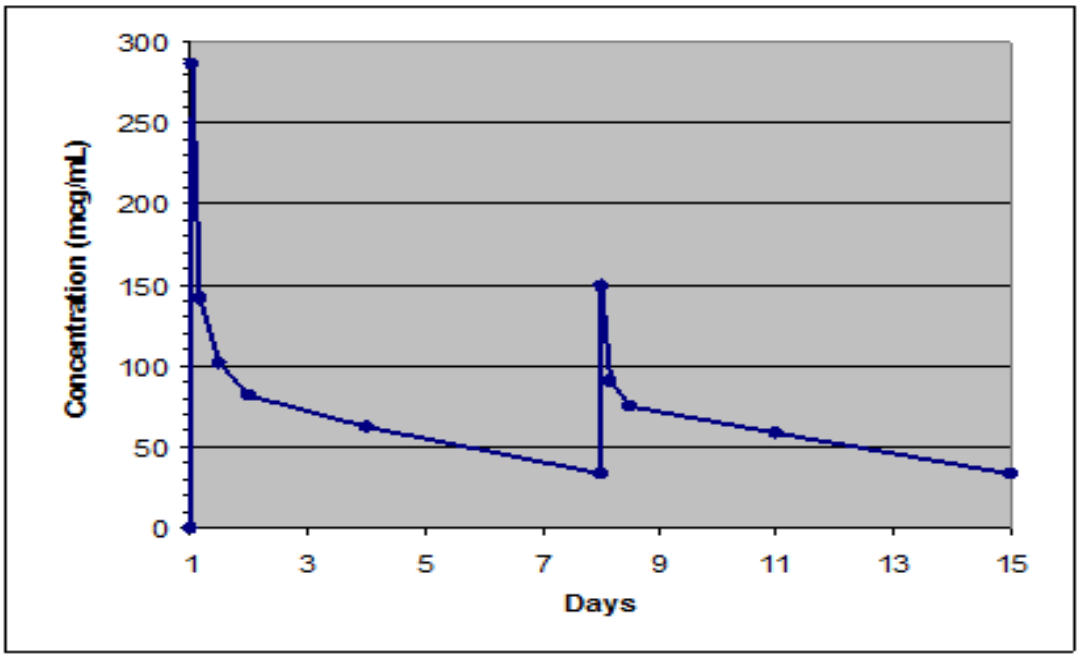


The excretion profile of dalbavancin compared to other glycopeptides is unique in that it has dual routes of excretion. By contrast, vancomycin is excreted almost entirely into urine (Evans 1992).

5.2.2 Pharmacokinetics in Healthy Volunteers

The PK of IV dalbavancin were studied in healthy subjects enrolled in single- and multiple-dose studies. Single-dose administrations ranged from 70 mg to 1500 mg, and multiple-dose regimens ranged from a total of 480 mg to 1600 mg administered over 7 days, and up to 4500 mg over up to 8 weeks. A representative plasma-concentration curve for the recommended 2-dose weekly therapeutic regimen of 1000 mg on Day 1 and 500 mg on Day 8 is shown in Figure 20.

Figure 20 Mean Dalbavancin Plasma Concentrations vs. Time in Healthy Subjects Following a 2-Weekly Dose Therapeutic Regimen



5.2.2.1 Special Pharmacokinetic Studies in Healthy Volunteers

Dalbavancin was evaluated for safety, tolerability and PK in healthy volunteers using dosing regimens that exceeded the recommended therapeutic dose regimen of 1000 mg on Day 1 and 500 mg on Day 8. In order to evaluate the effect on the QT/QTc interval, dalbavancin was also administered to healthy volunteers in 2 trials in which the entire recommended therapeutic dose regimen of 1500 mg was administered as a single dose (Studies DUR001-101 and DUR001-102), whereas a multiple dose regimen study evaluated weekly doses for up to 8 weeks (Study DUR001-104).

STUDY DUR001-101

This was a phase 1, open-label, single-dose, 1-period, 1-treatment study to determine plasma concentrations of dalbavancin administered intravenously to healthy adult male and female subjects under fasted conditions. PK parameters were assessed for 8 subjects and included AUC_{0-t}, C_{max}, and T_{max}. Mean PK parameters for dalbavancin in healthy subjects are summarized in Table 22. T_{max} occurred immediately following the end of the 30 minute infusion.

Table 22 Pharmacokinetic Parameters for Dalbavancin Following a Single 1500 mg IV Infusion to Healthy Subjects

Pharmacokinetic Parameter	Mean
AUC_{0-t} (mg·h/L)[a]	5202.55 (±620.05)
C_{max} (mg/L)[a]	467.63 (±55.73)
T_{max} (h)[b]	0.50 [0.50-0.50]

Source: DUR001-101 CSR
[a] Mean (±SD)
[b] Mean [Range]

Abbreviations: AUC_{0-t} = area under the plasma concentration versus time curve from 0 to t; C_{max} = maximum plasma drug concentration; IV = intravenous; SD = standard deviation; T_{max} = time of maximum plasma drug concentration

STUDY DUR001-102

This was a phase 1, single-center, randomized, single-dose, placebo- and positive-controlled, partially double-blind, parallel group electrocardiographic study to evaluate single IV doses of 1000 mg (therapeutic dose) and 1500 mg (supratherapeutic dose) dalbavancin. Healthy adult subjects were enrolled and randomly assigned to a single IV dose of dalbavancin 1000 mg, dalbavancin 1500 mg, or IV placebo, administered over 30 minutes, or IV placebo administered over 30 minutes with a single oral dose of moxifloxacin 400 mg tablet at the start of infusion. A total of 200 healthy adult subjects were enrolled and 199 subjects completed the study.

PK parameters were assessed for the 99 subjects who received dalbavancin and included AUC_{0-24h}, C_{max}, and $T_{max,}$ and are summarized in Table 23. Exposure over 24 hours and peak plasma concentrations increased with dose in a proportional manner as observed by approximately 50% higher mean observed AUC_{0-24h} and C_{max} in subjects who received 1500 mg compared to those who received 1000 mg. For both dose groups, maximum dalbavancin plasma concentrations were reached at a median of 0.62 hours.

Table 23 Pharmacokinetic Parameters for Dalbavancin Following a Single 1000 mg and a Single 1500 mg IV Infusion to Healthy Subjects

Pharmacokinetic Parameter	Dalbavancin 1000 mg n=50	Dalbavancin 1500 mg n=49
AUC_{0-24h} (mg·h/L)[a]	3184.82 (12.76)	4836.64 (13.71)
C_{max} (mg/L)[a]	287.32 (13.92)	422.57 (13.21)
T_{max} (h)[b]	0.62 [0.62-0.68]	0.62 [0.62-1.12]

[a] Mean (%CV)
[b] Mean [Range]

Abbreviations: AUC_{0-24h} = area under the plasma concentration versus time curve from 0 to 24h; C_{max} = maximum plasma drug concentration; CV = coefficient of variation; IV = intravenous; T_{max} = time of maximum plasma drug concentration

STUDY DUR001-104

This was an open-label, multiple-dose, parallel cohort study to evaluate the safety and PK of dalbavancin administered IV weekly for 4 to 8 weeks in healthy adult subjects. Subjects in this study were divided into 3 dosing cohorts. All subjects received 1000 mg dalbavancin administered IV over 30 minutes on Day 1 followed by 500 mg dalbavancin administered IV either on Days 8, 15, and 22 (Cohort I); Days 8, 15, 22, 29, and 36 (Cohort II); or Days 8, 15, 22, 29, 36, 43, and 50 (Cohort III). A total of 18 subjects were enrolled and completed the study.

PK parameters are summarized in Table 24. C_{min}, C_{max}, and $AUC_{0-\tau}$ were slightly higher after the administration of 6 or 8 total weekly infusions of dalbavancin relative to Cohort I, but no significant differences in PK parameters were observed when comparing Cohort II and Cohort III. Accumulation ratios were comparable between all cohorts and no apparent accumulation was observed. PK parameters assessed after the single 1000 mg dalbavancin dose administered on Day 1 were consistent across cohorts.

Table 24 Pharmacokinetic Parameters of Dalbavancin Following Multiple and Increasing Dosing Durations in Healthy Subjects

Pharmacokinetic Parameter	Cohort I (4 Total Infusions) n=6	Cohort II (6 Total Infusions) n=6	Cohort III (8 Total Infusions) n=6
$AUC0_{-\tau}$ (mg·h/L)a	10202.82 (14.92)	12992.79 (17.76)	12173.30 (17.70)
C_{max} (mg/L)a	160.00 (13.99)	187.00 (13.05)	179.67 (11.02)
T_{max} (h)b	0.50 [0.50 – 1.00]	0.50 [0.50 – 0.55]	0.50 [0.50 – 1.00]
$t_{1/2}$ (h)[a]	98.88 (10.11)	98.89 (9.71)	109.04 (14.62)

[a] Mean (%CV)
[b] Median [Range], from Day 1 single 1000 mg dose

Abbreviations: $AUC_{0-\tau}$ = area under the plasma concentration versus time curve over the final day dosing interval at steady-state; C_{max} = maximum plasma drug concentration over the final dosing interval; CV= coefficient of variation; T_{max} = time of maximum plasma drug concentration; $t_{1/2}$= terminal elimination half-life.

5.2.3 Special Populations

5.2.3.1 Race and Ethnicity

STUDY DUR001-103

This was a phase 1, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK of single IV doses of 500 mg and 1000 mg dalbavancin in healthy male and female Japanese subjects. Subjects were enrolled and randomized to receive a single IV dose of 500 mg dalbavancin, 1000 mg dalbavancin, or placebo administered over 30 minutes. A total of 18 subjects were enrolled and completed the study.

PK parameters were assessed for the 15 subjects who received dalbavancin (5 subjects received 500 mg dalbavancin and 10 subjects received 1000 mg dalbavancin) and are summarized in Table 25. After a single dose IV infusion of dalbavancin, C_{max} and AUC increased in a proportional manner for the 500 mg and 1000 mg dose.
Maximum dalbavancin plasma concentrations were reached at 0.50 hours for the 500 mg dose and 0.81 hours for the 1000 mg dose. The mean $t_{½}$ was consistent across the 2 dose levels. CL and V_d were not dose dependent; mean CL ranged from 40.5 to 42.2 mL/hour and mean V_d ranged from 11301 to 12182 mL across the 2 dose levels.

Table 25 Pharmacokinetic Parameters for Dalbavancin Following a Single 500 mg and a Single 1000 mg IV Infusion to Healthy Japanese Subjects

Pharmacokinetic Parameter	Dalbavancin 500 mg n=5	Dalbavancin 1000 mg n=10
$AUC_{0\text{-}Day7}$ (mg·h/L) [a]	5790 (11.6)	12230 (12.0)
C_{max} (mg/L)[a]	158.2 (11.2)	301.2 (12.0)
T_{max} (h)[b]	0.50 [0.50-0.50]	0.81 [0.50–1.02]
$t_{1/2}$ (h)[a]	204 (13.3)	193.1 (9.1)

[a] Mean (%CV)
[b] Mean [Range]

Abbreviations: $AUC_{0\text{-}7}$ = area under the plasma concentration versus time curve from 0 to Day 7; C_{max} = maximum plasma drug concentration; IV = intravenous; SD = standard deviation; T_{max} = time of maximum plasma drug concentration; $t_{1/2}$ = terminal half life.

5.2.3.2 Pediatric Patients

STUDY A8841004

This was a phase 1, open-label, multicenter study to investigate the PK, safety and tolerability of a single dose of dalbavancin administered intravenously in hospitalized pediatric subjects, aged 12-16 years in addition to background anti-infective treatment for a known or suspected bacterial infection. A single dose of 1000 mg of dalbavancin was administered to subjects weighing ≥ 60 kg, and 15 mg/kg for subjects weighing < 60 kg, as a 30 minute IV infusion. A total of 10 subjects were enrolled and completed the study; 5 subjects received the 1000 mg dose of dalbavancin and 5 subjects received the 15 mg/kg dose.

PK parameters were assessed in all 10 subjects and are summarized in Table 26. C_{max} for both groups was comparable and occurred at the end of infusion. Total CL, renal clearance, and V_{dss} appeared to be marginally higher for subjects weighing ≥ 60 kg compared to subjects weighing < 60 kg.

Table 26 Pharmacokinetic Parameters for Dalbavancin Following a Single Dose in Hospitalized Pediatric Subjects Aged 12 to 16 Years

Pharmacokinetic Parameter	Dalbavancin 1000 mg n=5	Dalbavancin 15 mg/kg n=5
AUC_{Inf} (mg·h/L)[a]	17495 (28)	16248 (20)
C_{max} (mg/L)[a]	212 (12)	191 (27)
T_{max} (h)[b]	0.50 [0.47-1.00]	0.50 [0.47–1.00]
$T_{1/2}$ (h)[a]	227 (7)	202 (20)
CL (mL/hr)	57.2 (28)	48.1 (25)
CLr (mL/hr)[a]	15.7 (37)	9.97 (48)
Vss (mL)[a]	15232 (29)	11816 (11)

[a] Mean (%CV)
[b] Mean [Range]

Abbreviations: AUC_{Inf}= area under the plasma concentration versus time curve from 0 to infinite time; C_{max} = maximum plasma drug concentration; SD = standard deviation; T_{max} = time of maximum plasma drug concentration; $T_{1/2}$= terminal half-life.

5.2.3.3 Age and Gender

No individual studies to determine PK based on age and gender have been conducted.

5.2.3.4 Renal Impairment

STUDY VER001-3

This was a phase 1, double-blind, placebo-controlled, single-dose study conducted at a single site in the United States to assess the PK of dalbavancin in subjects with mild to moderate renal impairment. Subjects either received a single 70 mg dose of dalbavancin or matching placebo administered as a 30-minute IV infusion. The study was terminated early because of a sponsor decision to proceed with a higher, more clinically relevant dose. All subjects had mild renal impairment with CL_{Cr} rates ranging from 54.5 to 78.2 mL/min.

PK parameters were assessed in 3 subjects with mild renal impairment and are summarized in Table 27. Peak plasma concentrations were achieved immediately following the end of infusion. Dalbavancin had a V_d of approximately 11.1 L and was slowly eliminated with total drug CL in plasma of 0.0364 L/h.

Table 27 Pharmacokinetic Parameters for Dalbavancin Following a Single 70 mg IV Infusion to Subjects With Mild to Moderate Renal Impairment

Pharmacokinetic Parameter	Mean
AUC (mg·h/L)[a]	1970 (±373)
C_{max} (mg/L)[a]	22.4 (±6.24)
T_{max} (h)[b]	0.50 [0.50-0.50]
$T_{1/2}$ (h)[a]	247 (± 45)

[a] Mean (±SD)
[b] Mean [Range]

Abbreviations: AUC = area under the plasma concentration versus time curve from 0 to t; C_{max} = maximum plasma drug concentration; IV = intravenous; SD = standard deviation; T_{max} = time of maximum plasma drug concentration; $T_{1/2}$= terminal half-life.

STUDY VER001-11

This was a phase 1, open-label, single-dose study of dalbavancin administered intravenously as a 30-minute infusion to otherwise healthy subjects with severe renal impairment (CL_{Cr} < 30 mL/min) or end-stage renal disease (dialysis-dependent) and to subjects with normal renal function. Subjects with severe renal impairment received a single dose of dalbavancin (either 500 mg or 1000 mg). Subjects with end-stage renal disease received a single 500 mg dose of dalbavancin either before or after a dialysis session. Subjects with normal renal function received a single 500 mg dose of dalbavancin. A total of 22 subjects were enrolled and completed the study.

PK parameters were assessed in all 22 subjects and are summarized in Table 28. Through Day 7 postdose, dalbavancin plasma concentrations were similar among subjects with normal renal function and subjects with either severe renal impairment or end-stage renal disease who received the 500 mg dose and peak plasma concentrations occurred shortly after the end of infusion. A small but consistent increase in concentration beyond the first week postdose was observed in subjects with severe renal impairment.

Table 28 Pharmacokinetic Parameters for Dalbavancin Following a Single IV Infusion to Subjects With Severe Renal Impairment, End-Stage Renal Disease and Healthy Subjects.

Pharmacokinetic Parameter	Severe Renal Impairment[c] n=6	Severe Renal Impairment[d] n=4	End Stage Renal Disease: predialysis[c] n=3	End Stage Renal Disease: post-dialysis[c] n=3	Normal Renal Function[c] n=6
AUC_{0-7} (mg·h/L)[a]	6077 (± 1392)	10653 (± 1474)	6069 (± 1768)	4969 (± 1153)	5245 (± 1661)
C_{max} (mg/L)[a]	136.5 (± 21.6)	315.3 (± 89.7)	140.7 (± 26.4)	145.8 (± 71.5)	137.3 (± 39.5)
T_{max} (h)[b]	0.54 [0.52 – 0.65]	0.55 [0.50 – 0.60]	0.55 [0.50 – 0.62]	0.58 [0.50 – 0.65]	0.51 [0.50 – 0.52]
$T_{1/2}$ (h)[a]	454 (±102)	469 (±103)	376 (±63)	347 (±78)	333 (±91)

[a] Mean (±SD)
[b] Mean [Range]
[c] 500 mg dose
[d] 1000 mg dose

Abbreviations: AUC_{0-7} = area under the plasma concentration versus time curve from 0 to Day7; C_{max} = maximum plasma drug concentration; IV = intravenous; SD = standard deviation; T_{max} = time of maximum plasma drug concentration; $T_{1/2}$ = terminal elimination half-life.

STUDY VER001-13

This was a phase 1, open-label, single-dose study of dalbavancin administered intravenously to otherwise healthy subjects with mild (CL_{Cr} = 50 to 79 mL/min) and moderate (CL_{Cr} = 30 to 49 mL/min) renal impairment and to subjects with normal renal function. Subjects received a single 1000 mg dose of dalbavancin administered as a 30-minute IV infusion. A total of 21 subjects were enrolled and completed the study.

PK parameters were assessed in 9 subjects with normal renal function, 6 subjects with mild renal impairment, and 6 subjects with moderate renal impairment and are summarized in Table 29. Systemic exposure of dalbavancin was similar between subjects with normal renal function and subjects with mild renal function. An increased concentration and systemic exposure were observed in subjects with moderate renal impairment.

Table 29 Pharmacokinetic Parameters for Dalbavancin Following a Single 1000 mg IV Infusion to Subjects with Mild or Moderate Renal Impairment and Healthy Subjects.

Pharmacokinetic Parameter	Normal Renal Function n=9	Mild Renal Impairment n=6	Moderate Renal Impairment n=6
AUC (mg·h/L)[a]	24561 (± 5252)	27047 (± 4084)	37665 (± 7123)
C_{max} (mg/L)[a]	248.8 (± 33.0)	266.8 (± 42.3)	330.7 (± 55.7)
T_{max} (h)[b]	0.50 [0.52 – 1.00]	0.50 [0.50 – 0.55]	0.56 [0.50 – 1.22]
$T_{1/2}$ (h)[a]	417 (± 108)	389 (±59)	431 (±43)

[a] Mean (±SD)
[b] Mean [Range]

Abbreviations: AUC= area under the plasma concentration versus time curve from 0 to t; C_{max} = maximum plasma drug concentration; IV = intravenous; SD = standard deviation; T_{max} = time of maximum plasma drug concentration; $T_{1/2}$= terminal elimination half-life.

5.2.3.5 Hepatic Impairment

STUDY VER001-12

This was a phase 1, open-label, multiple-dose study of IV dalbavancin administered to subjects with mild, moderate or severe hepatic impairment and to subjects with normal hepatic function. Subjects received a 1000 mg dose of dalbavancin on Day 1 and a 500 mg dose of dalbavancin on Day 8 administered as a 30-minute infusion. A total of 27 subjects were enrolled and 26 completed the study.

PK parameters were assessed in 26 subjects and are summarized in Table 30. Dalbavancin administration to subjects with normal hepatic function and subjects with mild hepatic impairment resulted in comparable concentration-time profiles over the 60-day sampling interval. Dalbavancin administration to subjects with moderate hepatic impairment and to those with severe hepatic impairment resulted in slightly decreased observed concentrations when compared to subjects with normal hepatic function. Dalbavancin terminal half-life ($T_{1/2}$) was comparable across the 4 groups.

Table 30 Pharmacokinetic Parameters for Dalbavancin in Subjects With Mild, Moderate, or Severe Hepatic Impairment and Healthy Subjects

Pharmacokinetic Parameter	Mild Hepatic Impairment n=6	Moderate Hepatic Impairment n=6	Severe Hepatic Impairment n=5	Normal Hepatic Function n=9
AUC_{0-8} (mg·h/L)[a]	11146 (±3478)	7710 (± 1099)	7561 (± 1540)	10577 (± 2493)
C_{max} (mg/L)[a]	331.7 (± 80.6)	227.2 (± 37.5)	199.0 (± 30.4)	278.3 (± 52.6)
T_{max} (h)[b]	0.53 [0.52 – 0.55]	0.52 [0.52 – 0.53]	0.54 [0.52 – 0.63]	0.52 [0.52 – 0.53]
$T_{1/2}$ (h)[a]	323 (± 27)	320 (± 24)	322 (± 68)	321 (± 24)

[a] Mean (±SD)
[b] Mean [Range]

Abbreviations: AUC_{0-8} = area under the plasma concentration versus time curve from 0 to Day8; C_{max} = maximum plasma drug concentration after first dose; SD = standard deviation; T_{max} = time of maximum plasma drug concentration after first dose; $t_{1/2}$ = terminal elimination half-life.

5.2.4 Population Pharmacokinetics

In addition to the phase 1 PK studies described above, plasma concentrations were also collected in patient studies and analyzed together using population PK. The PK of dalbavancin had low inter-individual variability, were predictable and consistent with dose proportionality, and found to be similar between patients and subjects. Three separate population PK analyses have been conducted for dalbavancin using datasets of pooled data from various PK studies. Additionally, PK/PD analyses have been conducted for dalbavancin using exposure estimates or Monte Carlo simulations based upon the population PK modeling. A description of the various population PK analyses is presented below:

- Study VER001-PK-001: The primary objective of the analysis was to determine the statistical significance of potential covariates in relation to the inter-individual variability in dalbavancin population PK parameters. The following covariates were tested in the population-based covariate analysis: body weight, body surface area (BSA), gender, race, age, creatinine clearance (CL_{Cr}), serum albumin and concomitant medications. In the final model, accounting for fixed effects, the interpatient variability in CL was estimated to be 18%. The significant covariate relationships only described ~10% of the inter-individual variability in CL. This population PK analysis also examined the effect of concomitant medications on dalbavancin PK, and the results are used to support the discussion of potential drug-drug interactions in Section 8.4.6.7 of this document.
- Study VER001-PK-002 utilized the inputs for the simulations included the population PK parameter estimates from the model developed in VER001-PK-001 and a distribution of MIC values derived from 3 phase 3 skin infection trials (VER001-8, VER001-9, and VER001-16). Although these simulations provided valuable information regarding the chosen clinical dosage regimen at the time, PK/PD target attainment simulations have been updated using current MIC surveillance data and a more robust population PK model (ie, using a larger population PK database for dalbavancin).

- The Projections Analysis Report involved refinement of the population PK model described in VER001-PK-001 using the same population PK dataset (ie, PK-related data drawn from studies VER001-4, VER001-5, and VER001-9). The primary goal of the analysis was to refine the structure of the population PK model and re-examine covariate relationships from the previous analysis. The results of these analyses were used to support dosage recommendations for special populations (Section 5.2.3).
- The analyses reported in ICPD-00280 included the application of the Projections Research population PK model to phase 3 data in order to estimate exposure in patients who received dalbavancin and underwent sparse PK sampling in VER001-9. The PK exposures were then used in a PK/PD analysis to examine relationships between dalbavancin PK exposure and outcome. Monte Carlo simulation analyses were also conducted to assess PK/PD target attainment using both animal- and clinically-derived PK/PD targets for efficacy. The results of these analyses were used to support the proposed clinical dosage regimen.

5.2.5 Comparison of the Pharmacokinetics of Dalbavancin with US-Marketed Glycopeptides

The PK of dalbavancin are distinctive compared with the 2 US-marketed glycopeptides, vancomycin and telavancin.

Vancomycin is marketed in the United States and Europe and has a $T_{1/2}$ of 4 to 6 hours and a mean plasma CL of 0.058 L/h/kg (Vancomycin Prescribing Information). The majority of administered drug is excreted in the urine with a mean renal CL of 0.048 L/h/kg. The drug is approximately 55% serum protein-bound. The shorter vancomycin $T_{1/2}$ requires the drug to be administered at least twice daily in order to maintain concentrations above therapeutic levels. However, for patients with impaired renal function, $T_{1/2}$ is significantly prolonged and the total body CL is reduced (Evans 1992). The prolonged $T_{1/2}$ observed for vancomycin in subjects with a CL_{Cr} of <10 mL/min is approximately 6 days (Matzke 1984) and similar to the predominant $t_{1/2}$ observed for dalbavancin. Vancomycin PK are influenced by renal impairment and other diseases, and are markedly changed in geriatric patients and in burn patients (Evans 1992; Matzke 1984; Cutler 1984; Rybak 1990). These factors influence the inter-patient variability observed for vancomycin, which is larger than that described for dalbavancin. In many cases, the larger interpatient variability combined with a narrow therapeutic window require drug monitoring for vancomycin, and subsequent dosage adjustment throughout therapy (Evans 1992).

Telavancin PK are similar to that of vancomycin (Vibativ® Prescribing Information). Telavancin has a relatively short $T_{1/2}$ (approximately 8 hours). Similar to vancomycin, the effects of renal impairment are more pronounced than that observed for dalbavancin; in a phase 1 renal impairment study, the mean $AUC_{0\text{-inf}}$ values were approximately 13%, 29%, and 118% higher for subjects with CL_{Cr} > 50 to 80 mL/min, CL_{Cr} > 30 to 50 mL/min, and $CL_{Cr} \leq 30$ mL/min, respectively. Due to the reduced clearance of telavancin in patients with renal impairment, dosage adjustments are recommended in patients with a $CL_{Cr} \leq 50$ mL/min. Three metabolites of telavancin were observed in a mass balance study; these

metabolites accounted for < 10% of the radioactivity in urine and < 2% of the radioactivity in plasma.

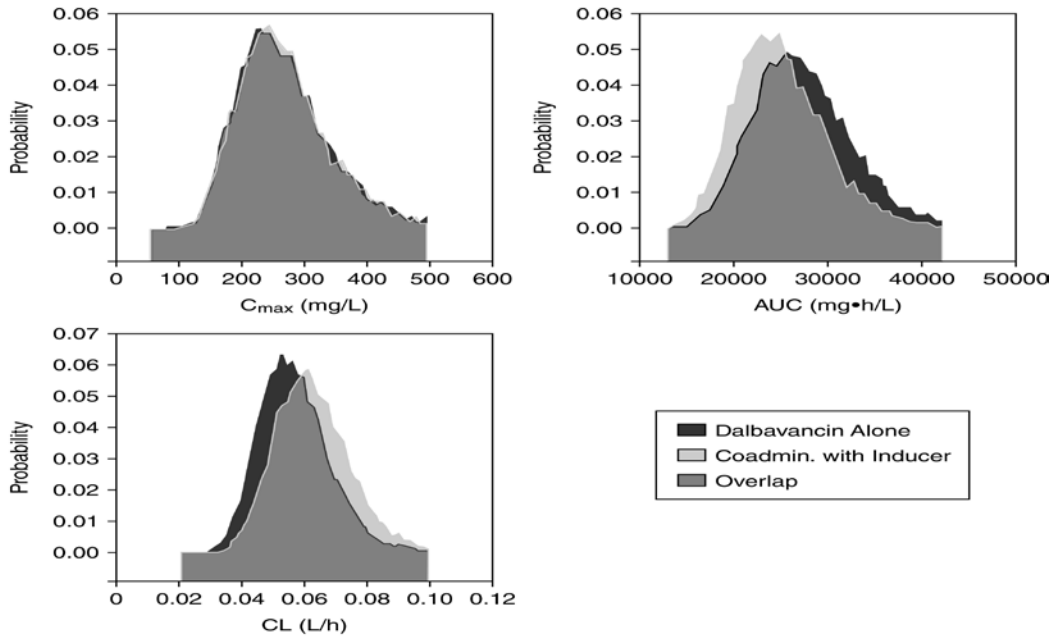
5.3 Potential for Drug-Drug Interactions

Dalbavancin has a low potential for drug-drug interactions. No interference of dalbavancin with CYP450 enzymes have been observed in vitro or in vivo. Studies in humans and animals have shown that the majority of administered dose is excreted as intact drug by both renal and non-renal routes.

As there were no indications from nonclinical or clinical studies of any specific drug-drug interaction, no specific clinical drug-drug interaction studies were performed. However, as suggested by regulatory guidance (*Population Pharmacokinetics*, 1999; *Drug Interaction Studies--Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations* 2012), and advice from the DAIP, in situations for which there is no indication of a drug-drug interaction, population PK was used to screen for possible interacting concomitant drugs.

A population PK analysis (Section 5.2.4) was performed using data from 3 studies in patients. A total of 1668 dalbavancin concentration observations from 532 patients were included in the analysis. The only statistically significant variable was the presence of CYP450 inducers. The presence of CYP450 substrates, inhibitors, or any of the individual concomitant medications had no significant effect on the CL of dalbavancin. The presence of an inducer increased the CL of dalbavancin by < 10%, showing the sensitivity of the population analysis in screening for possible drug-interacting covariates. Subsequent Monte Carlo simulations showed a great amount of overlap in the distribution of the PK parameters (C_{max}, AUC, and CL) when dalbavancin is administered alone compared to when administered with an inducer (Figure 21). All comparisons showed the 90% confidence intervals fall completely within the 80% to 125% bioequivalence range, indicating that coadministration of dalbavancin and a CYP450 inducer had no clinically significant interaction.

Figure 21 Simulated Distributions of Dalbavancin C_{max}, AUC, and CL With and Without Co-Administration of an Inducer



5.4 Pharmacokinetic-Pharmacodynamic Relationships

5.4.1 Dose Regimen Justification for Achievement of Clinical Efficacy

The studies of the primary PD of dalbavancin show the drug to be active against most Gram-positive bacterial species, including strains resistant to other antibiotic classes, and is also active against some organism groups that are resistant to vancomycin (Section 7). A summary of dalbavancin PD is provided in Section 4.1.1. Investigation of the PK/PD relationship in a mouse neutropenic thigh model demonstrated the AUC:MIC ratio to be an important parameter in the efficacy of the drug. This study also showed that larger amounts of the drug dosed infrequently produced better efficacy than smaller more frequent doses.

PK/PD analyses were carried out using data from dalbavancin-treated patients from Study VER001-9 (ICPD-00280). Patients in the dalbavancin arm received a 1000 mg IV dose on Day 1 followed by a 500 mg IV dose on Day 8. Using Bayesian post-hoc estimates for these patients derived from the previously-described population PK model (Projections Analysis), $AUC_{0\text{-}120}$ was estimated for each patient. The average daily AUC, derived by dividing the $AUC_{0\text{-}120}$ by 5, was then indexed to the MIC of the baseline pathogen (AUC_{avg}:MIC ratio); this index served as the primary measure of drug exposure in the PK/PD analyses. Efficacy endpoints assessed for the PK/PD analyses included clinical and microbiological response at EOT (within 3 days of completion of study medication) and test-of-cure, TOC (14 days ±2 days after completion of study medication). Univariable relationships for these efficacy endpoints were examined using chi-square or Fisher's exact tests for categorical forms of AUC_{avg}:MIC ratio and logistic regression for AUC_{avg}:MIC ratio evaluated as a continuous variable. Multivariable analyses were considered for each efficacy endpoint if a statistically

significant ($p<0.05$) or borderline-significant ($p=0.05$ to 0.1) biologically plausible univariable relationship between AUC_{avg}:MIC ratio and the given efficacy endpoint was identified.

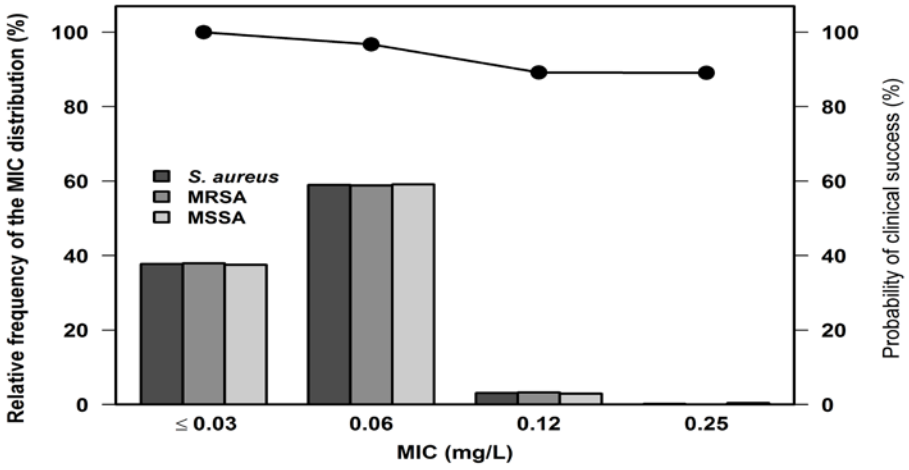
Results of the above-described PK/PD analyses in all microbiologically evaluable patients (n=192) or patients with *S. aureus* isolated at baseline (n=177) revealed statistically significant and borderline-significant univariable relationships between clinical and microbiological response at EOT and TOC and AUC_{avg}:MIC ratio. AUC_{avg}:MIC ratios exceeding thresholds ranging from 13,658 to 21,267 were associated with a higher percentage successful clinical or microbiological response at EOT or TOC. Multivariable analyses demonstrated retention of AUC_{avg}:MIC ratio as a significant variable when evaluated with other independent variables for the majority of these models.

Given that the percentage of patients achieving the above-described AUC_{avg}:MIC ratio thresholds was higher compared to those not achieving these thresholds for most of the efficacy endpoints evaluated, these data provide support for the dalbavancin dosing regimen of 1000 mg IV dose on Day 1 followed by a 500 mg IV dose on Day 8. When coupled with the high rates of efficacy and favorable safety profile (which was similar to those receiving the comparator agent, linezolid), the data from the dalbavancin arm of Study VER001-9 provide support for both the efficacy and safety of this dosing regimen.

Using the above-described PK/PD relationships for efficacy, parameter estimates from the previously-developed population PK model for dalbavancin, and Monte Carlo simulation, further analyses were conducted to provide support for establishing *S. aureus* in vitro susceptibility interpretive criteria for dalbavancin. The first step involved generating a population of 5,000 simulated patients with covariates included in the population PK model and with distributions based on data from patients with ABSSSI. Using the simulated patient demographics, fixed and random effects parameter estimates for the population PK model, and Monte Carlo simulation techniques, the second step involved generating PK parameter estimates for each simulated patient. The parameter estimates were used to generate plasma concentration-time profiles from time zero to 120 hours for each patient following dalbavancin 1000 mg (or 750 mg for patients with $CL_{Cr} < 30$ mL/min) on Day 1. The $AUC_{0\text{-}120}/5$ (AUC_{avg}) was calculated and then divided by MIC values ranging from 0.03 to 0.25 mg/L.

The mean model-predicted percent probability of a successful clinical response was determined by MIC value using the PK/PD relationship for clinical response at TOC based on data from patients with *S. aureus* at baseline (n=177). The relationship between clinical response at TOC and AUC_{avg}:MIC ratio evaluated as a 2-group variable was based on AUC_{avg}:MIC ratio threshold of 21,267. The percent (n/N) of successful clinical responses for those patients < and ≥ this threshold was 89.1% (98/110) and 100% (52/52), respectively ($p=0.01$). Mean percent probabilities of clinical success by MIC based on this PK/PD relationship overlaid on a MIC distribution for *S. aureus*, MRSA and MSSA (Jones, et al. 2011) are shown in Figure 22. The mean percent probability of a successful clinical response exceeded or approached 90% up to a MIC value of 0.25 mg/L. Results of these analyses provide support for the establishing in vitro interpretive criteria for dalbavancin against *S. aureus*.

Figure 22 Mean Percent Probabilities of Clinical Success by MIC Overlaid Over the MIC Distributions for *S. aureus*, MRSA, and MSSA



5.4.2 Pharmacokinetic-Pharmacodynamic Relationships Regarding Efficacy

The majority of ABSSSI infections are caused by Gram-positive pathogens, predominantly *S. aureus* (including strains resistant to currently available antimicrobial agents) and β-hemolytic streptococci (Section 7.2.1). Extensive surveillance and other in vitro studies demonstrated consistent potency of dalbavancin against these and other Gram-positive species. Dalbavancin MIC distributions did not vary among geographical regions, between clinical and surveillance studies, or over time.

Several animal infection studies were conducted with *S. aureus*, including MRSA and VISA strains. Because there are few infection models with β-hemolytic streptococci, animal studies were also performed using *S. pneumoniae*, which is a highly virulent organism in the mouse. *S. aureus* and *S. pneumoniae* were utilized for PK/PD modeling in the neutropenic mouse thigh model.

Dalbavancin has a long $T_{1/2}$ in animals and humans, a time-dependent bactericidal activity in vitro, and has been shown to be more efficacious in animal models when administered as larger, less frequent dosages. Levels of unbound dalbavancin exceed bactericidal concentrations throughout the proposed 14-day, 2 weekly-dose treatment period. These features suggested that T>MIC might be a contributing PD parameter to its efficacy. However, AUC/MIC correlated with efficacy in the neutropenic mouse thigh model and has been used in PK/PD analyses leading to target attainment estimates and determination of susceptibility interpretive criteria (Section 7.5).

6 CLINICAL EFFICACY

6.1 Overview of the Dalbavancin Clinical Development Program

The clinical development of dalbavancin was performed in concordance with standard approaches as used for the evaluation of newer antibacterial agents, including written regulatory guidances in effect at the time the trials were conducted, as well as following scientific advice from health authorities in the United States and the EU.

All studies were conducted in accordance with the ICH Guidelines for Good Clinical Practice and the Declaration of Helsinki. All trials were conducted with emphasis on risk minimization and protection of human subjects, including review by duly-constituted Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). Informed consent was obtained from all study subjects.

All studies were subject to regular monitoring by the Sponsor or an appointed Contract Research Organization. Data collection and analyses were performed according to standard practices, in consistency with prospectively-defined endpoints defined in Statistical Analysis Plans (SAPs).

6.1.1 Durata Therapeutics Interactions with Regulatory Agencies

Interactions with the US Food and Drug Administration (FDA)

In August 2010, the FDA issued a new applicable draft Guidance for the treatment of ABSSSI (Appendix 1). In this guidance,the indication of uSSSI/cSSSI was replaced by ABSSSI, which was divided into 2 general categories: (1) ABSSSI, for which a reliable estimate of a treatment effect of antibacterial drug therapy can be described and either noninferiority or superiority trial designs were recommended; and (2) milder skin infections for which a treatment effect of antibacterial drug therapy has not been characterized and superiority trial designs were recommended. In October 2013, the Guidance for ABSSSI was finalized (Appendix 2), and the minor cutaneous lesions described above, as well as burn infections, were excluded from the ABSSSI category in the final Guidance. Patients with such infections were not to be enrolled in ABSSSI clinical trials.

ABSSSI overlaps considerably with what was previously described as cSSSI, but it also includes cellulitis/erysipelas, defined as "a diffuse skin infection characterized by spreading areas of redness, edema, and/or induration of a minimum surface area of 75 cm^2 (eg, length of 15 cm and width of 5 cm), accompanied by lymph node enlargement or systemic symptoms such as fever ≥ 38°C (100.4°F). During End-of-phase 2 discussions, Durata and the Agency initially concurred that cSSSI Study VER001-9 from the original Application, plus a second study DUR001-301, in accordance with the draft 2010 Guidance, would provide clinical experience to support an approvable registration package. Subsequently, Durata proposed, and the Agency agreed, that a 3rd trial, DUR001-302, identical in design to DUR001-301, would provide a more robust clinical package to demonstrate efficacy in ABSSSI. Durata requested Special Protocol Assessments (SPAs) from the Agency for the 2 new studies, for which the FDA provided agreements to both study protocols.

6.1.2 Proposed Indication

Dalbavancin for Injection is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) as caused by susceptible strains of the following Gram-positive microorganisms:

- *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains)
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*)

6.1.3 Clinical Development Strategy

Twenty-one clinical trials were conducted with dalbavancin in the entire clinical program, including the following:

- Fourteen phase 1 studies to determine the initial safety and tolerability profile in healthy volunteers and special populations, including those with renal or hepatic impairment, adolescents aged 12 to 16 years, and healthy native Japanese adults.
- Two phase 2 studies to elucidate the compound's potential utility in SSSI via assessment of 2 different dose regimens of dalbavancin in patients with SSSI and for the treatment of catheter-related bloodstream infections (CRBSI). This latter indication is not being pursued at the present time.
- Five phase 3 studies. The initial phase 3 program conducted by Vicuron, Inc. evaluated dalbavancin therapy in 3 studies of both cSSSI and uSSSI in patients who warranted parenteral therapy, with particular attention to those SSSI caused by MRSA. Durata Therapeutics subsequently conducted 2 additional phase 3 clinical studies that evaluated dalbavancin therapy for the treatment of ABSSSI.

The studies conducted during phase 1 of the development program are summarized in Section 5. The studies conducted in the phase 2/3 development program are summarized in Table 31.

Table 31 Efficacy Studies Conducted During Phase 2/3 Development of Dalbavancin

Study Number and Title	Treatment	Total Dosed	Enrolled in Dalbavancin group
Phase 3 Efficacy Studies			
DUR001-301 A phase 3, randomized, double-blind, double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin with possible switch to oral linezolid) for the treatment of acute bacterial skin and skin structure infections.	**IV Dalbavancin:** 1000 mg on Day 1, 500 mg dose on Day 8, IV placebo q12h to match vancomycin, possible switch to oral placebo q12h after 3 days of IV therapy, treatment duration 10-14 days. **IV Comparator:** IV vancomycin 1000 mg or 15 mg/kg q12h, IV placebo to match dalbavancin, possible switch to oral linezolid 600 mg q12h after 3 days of IV vancomycin therapy, treatment duration 10-14 days.	568	288
DUR001-302 A phase 3, randomized, double-blind, double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin with possible switch to oral linezolid) for the treatment of acute bacterial skin and skin structure infections.	**IV Dalbavancin:** 1000 mg on Day 1, 500 mg dose on Day 8, IV placebo q12h to match vancomycin, possible switch to oral placebo q12h after 3 days of IV therapy, treatment duration 10-14 days. **IV Comparator:** IV vancomycin 1000 mg or 15 mg/kg q12h, IV placebo to match dalbavancin, possible switch to oral linezolid 600 mg q12h after 3 days of IV vancomycin therapy, treatment duration 10-14 days.	735	371
VER001-9 A phase 3, randomized, double-blind, multi-center study to evaluate the safety and efficacy of dalbavancin versus linezolid in the treatment of complicated skin and soft tissue infections with suspected or confirmed Gram-positive bacterial pathogens.	**IV Dalbavancin:** 1000 mg on Day 1, 500 mg on Day 8, possible switch to oral placebo q12h, treatment duration 14 days. **IV Linezolid:** 600 mg q12h. Possible switch to oral linezolid 600 mg q12h, treatment duration 14 days.	854	571

Table 31 Efficacy Studies Conducted During Phase 2/3 Development of Dalbavancin

Study Number and Title	Treatment	Total Dosed	Enrolled in Dalbavancin group
Supporting Efficacy Studies			
VER001-5 A phase 2, pilot, randomized, open label, multi-center study to evaluate the safety and efficacy of dalbavancin versus investigator/physician-designated comparator in skin and soft tissue infection	**IV Dalbavancin:** Single dose [n=20]: 1100 mg on Day 1; Multiple dose [n=21]: 1000 mg on Day 1, 500 mg on Day 8. 1000 mg [n=1], 1100 mg [n=20], 1500 mg [n=20]. **IV Comparator:** Standard Antibiotic Therapy: as defined by investigator prior to randomization, given for 7 to 21 days.	62	41
VER001-8 A phase 3, randomized, double-blind, multi-center study to evaluate the safety and efficacy of dalbavancin versus cefazolin in the treatment of uncomplicated skin and soft tissue infection with suspected or confirmed Gram-positive bacterial pathogens	**IV Dalbavancin:** 1000 mg on Day 1, option to add 500 mg dose on Day 8, possible switch to oral placebo q6h, treatment duration 7 or 14 days. 1000 mg [n=273], 1500 mg [n=94]. **IV Comparator:** IV Cefazolin: 500 mg q8h, possible switch to oral cephalexin 500 mg q6h, treatment duration 7 or 14 days.	553	367
VER001-16 A phase 3, randomized, open-label, multi-center study to evaluate the safety and efficacy of dalbavancin vs. vancomycin in the treatment of complicated or uncomplicated skin and soft tissue infections with suspected or confirmed methicillin resistant *Staphylococcus aureus* (MRSA)	**IV Dalbavancin:** 1000 mg on Day 1, 500 mg on Day 8 (optional for uSSSI), 1000 mg [n=50], 1500 mg [n=57]. **IV Comparator:** IV Vancomycin: 1000 mg q12h, or dose-adjusted for renal impairment; possible switch to oral therapy for 14 days. Possible switch to cephalexin 500 mg q6h if subject did not have MRSA.	156	107

Table 31 Efficacy Studies Conducted During Phase 2/3 Development of Dalbavancin

Study Number and Title	Treatment	Total Dosed	Enrolled in Dalbavancin group
VER001-4 A phase 2, randomized, open-label, multi-center study to evaluate the safety and efficacy of dalbavancin versus vancomycin in the treatment of catheter- related bloodstream infections with suspected or confirmed Gram-positive bacterial pathogens.	**IV Dalbavancin:** Weekly: 1000 mg on Day 1, 500 mg on Day 8 (n=33). Daily: 650 mg on Day 1, 65 mg on Days 2-14 (this arm was discontinued) [n=7]. 780 mg [n=1], 845 mg [n=1], 1000 mg [n=3], 1170 mg [n=1], 1500 mg [n=34]. **IV Comparator:** IV vancomycin: 1000 mg q12h, or dose-adjusted for renal impairment. Could switch to IV nafcillin or oxacillin 2 g q4h or q6h after pathogen identification and susceptibility testing.	74	40
TOTAL		3002	1785

Note: IV and oral placebo was also used for blinding purposes.
Abbreviations: IV = intravenous; q4h = every 4 hours; q6h = every 6 hours; q12h = every 12 hours

6.2 Trial Design

6.2.1 Dose Selecton Rationale

The selection of a 2-dose weekly dosage regimen was based on animal and human pharmacology and PD studies (Sections 4.1, 4.2 and 5.2). Dalbavancin PK are linear, and the inter-patient variability is low, allowing for a once-weekly dosing regimen with no requirement for therapeutic drug monitoring. The 8.5 day β $t_{1/2}$ of dalbavancin (Section 5.2) allows for the utilization of a 2-dose weekly treatment regimen, potentially reducing the requirement for indwelling catheters, as compared to standard antibiotic treatment regimens, and the subsequent risk of catheter-related infection. Additionally, the use of 2 infusions 1 week apart may eliminate the need for subsequent continuation on oral antibiotic therapy (a situation in which patient compliance can be an issue), eliminate the need for, and the complications associated with, an indwelling IV catheter including PICC or mid-lines, and reduce the need for daily outpatient IV therapy, all without compromising either clinical efficacy or safety relative to approved agents.

The doses used in the phase 2/3 clinical development program are summarized in Table 32. In the pivotal trials, the dalbavancin regimen utilized the same 1000 mg on Day 1, followed by 500 mg on Day 8 regimen. Each dose was administered intravenously over 30 minutes. Patients with severe renal impairment (CL_{Cr} < 30 mL/min) and not receiving regular renal dialysis were administered 750 mg on Day 1 and 375 mg on Day 8.

Table 32 Dose Regimens in the Dalbavancin Phase 2/3 Program

Study Number	Dalbavancin Doses Administered	Number of Patients Treated with Dalbavancin
Pivotal phase 3 studies		
DUR001-301	1000 mg on Day 1; 500 mg on Day 8	284
DUR001-302	1000 mg on Day 1; 500 mg on Day 8	368
Additional phase 3 Study Relevant to the Claimed Indication		
VER001-9	1000 mg on Day 1; 500 mg on Day 8	571
Supportive phase 2/3 studies		
VER001-16	1000 mg on Day 1; 500 mg on Day 8	107
VER001-8	1000 mg on Day 1; option to add 500 mg dose on Day 8	367
VER001-5	1000 mg on Day 1; 500 mg on Day 8	41
VER001-4	1000 mg on Day 1;500 mg on Day 8	40

6.2.2 Patient Selection Criteria

The phase 3 clinical development program for dalbavancin involved treatment of ABSSSI or cSSSI.

6.2.2.1 ABSSSI Studies: DUR001-301 and DUR001-302

In the 2 pivotal ABSSSI Studies DUR001-301 and DUR001-302, the other inclusion and exclusion criteria are summarized in Table 33. Key inclusion and exclusion criteria for Study VER001-9 are described in Section 6.2.2.2.

Table 33 Inclusion/Exclusion Criteria Common to Phase 3 Studies DUR001-301, and DUR001-302

Inclusion Criteria
Male or female patients 18 to 85 years of age with ABSSSI, defined as an infection known or suspected of being caused by Gram-positive bacteria.
Major cutaneous abscess characterized as a collection of pus within the dermis or deeper that was accompanied by erythema, edema and/or induration which required surgical incision and drainage, and was associated with cellulitis such that the total affected area involved at least 75 cm^2 of erythema, and was defined by a margin of erythema that was total affected area involved at least 75 cm that was accompanied by erythemavention roved agents. , or, alternatively, involved the central face and was associated with an area of erythema of at least 50 cm^2 and a margin ively, involvdirections from the abscess rim, OR Surgical site or traumatic wound infection characterized by purulent drainage with surrounding erythema, edema, and/or induration which occurred within 30 days after the trauma or surgery and was associated with cellulitis such that the total affected area involved at least 75 cm^2 of erythema, and was defined by a margin of erythema in at least 1 direction that was ≥ 5 cm from the edge of the wound, or alternatively, involved the central face and was associated with an affected area of at least 50 cm^2 and had a margin of erythema in at least 1 direction ≥ 3 cm from the wound edge, OR Cellulitis, defined as a diffuse skin infection characterized by spreading areas of erythema, edema, and/or induration and was associated with erythema that involved at least 75 cm2 of surface area, or alternatively, cellulitis of the central face that was associated with an affected area of at least 50 cm^2.
A minimum surface area of redness, edema, and/or induration (ie, 75 cm^2 of cellulitis) either involving either deeper soft tissue or, if associated with abscess formation, requiring significant surgical intervention.
Two or more of the following signs of ABSSSI: (1) Purulent drainage/discharge; (2) Fluctuance; (3) Heat/localized warmth; (4) Tenderness to palpation; (5) Swelling/induration
One or more of the following systemic signs of infection: (1) elevated body temperature ≥38°C/100.4°F as measured by the patient/caregiver or investigator within 24 hours of Baseline; (2) White blood cell (WBC) count >12,000 cells/mm3; (3) manually performed WBC differential count with ≥10% band forms, regardless of peripheral WBC count
Infection severity such that a minimum of 3 days of IV therapy was appropriate for management of the ABSSSI
Exclusion Criteria
Contraindication to the administration of dalbavancin, vancomycin, or linezolid, such as hypersensitivity to any of the agents

Table 33 Inclusion/Exclusion Criteria Common to Phase 3 Studies DUR001-301, and DUR001-302

Females of childbearing potential who were unable to take adequate contraceptive precautions, had a positive pregnancy result within 24 hours prior to study entry, were known to be pregnant, or were currently breastfeeding an infant.
Patients with sustained shock, defined as systolic blood pressure < 90 mm Hg for more than 2 hours despite adequate fluid resuscitation, with evidence of hypoperfusion or need for sympathomimetic agents to maintain blood pressure.
Participation in another study of an investigational drug or device within 30 days before this study began.
Exclusion Criteria (continued)
Receipt of a systemically or topically administered antibiotic with a gram-positive spectrum that achieved therapeutic concentrations in the serum or at the site of the ABSSSI within 14 days prior to randomization. An exception was allowed for patients receiving a single dose of a short-acting (half-life ⩽12 hours) antibacterial drug ⩾3 days prior to randomization (eg., administration of a single dose of an antibacterial drug for surgical prophylaxis).
Infection due to an organism known prior to study entry to be resistant to dalbavancin or vancomycin (vancomycin minimum inhibitory concentration [MIC] > 8 µg/mL).
Patients with evidence of meningitis, necrotizing fasciitis, gas gangrene, gangrene, septic arthritis, osteomyelitis; endovascular infection, such as clinical and/or echocardiographic evidence of endocarditis or septic thrombophlebitis
Infections caused exclusively by gram-negative bacteria (without gram-positive bacteria present) and infections caused by fungi, whether alone or in combination with a bacterial pathogen.
Venous catheter entry site infection.
Infections that involved diabetic foot ulceration, a perirectal abscess or a decubitus ulcer.
An infected device, even if the device was removed.
Gram-negative bacteremia, even in the presence of gram-positive infection or gram-positive bacteremia.
ABSSSI was the result of having sustained full or partial thickness burns.
Infection involving a limb with evidence of critical ischemia of an affected limb defined as any of the following criteria: absent or abnormal Doppler wave forms, toe blood pressure of <45 mm Hg, ankle brachial index <0.5, and/or critical ischemia as assessed by a vascular surgeon.
Patients with ABSSSI such as superficial/simple cellulitis/erysipelas, impetiginous lesion, furuncle, or simple abscess that only required surgical drainage for cure.
Concomitant condition requiring any antibiotic therapy that would have interfered with the assessment of study drug for the condition under study.
Anticipated need of antibiotic therapy for longer than 14 days.
Patients who were placed in a hyperbaric chamber as adjunctive therapy for the ABSSSI.

Table 33 Inclusion/Exclusion Criteria Common to Phase 3 Studies DUR001-301, and DUR001-302

More than 2 surgical interventions (defined as procedures conducted under sterile technique and typically unable to be performed at the bedside) for the ABSSSI, or patients who were expected to require more than 2 such interventions.
Medical conditions in which chronic inflammation may have precluded assessment of clinical response to therapy even after successful treatment (eg., chronic stasis dermatitis of the lower extremity).
Medical conditions in which chronic inflammation may have precluded assessment of clinical response to therapy even after successful treatment (eg., chronic stasis dermatitis of the lower extremity).
Absolute neutrophil count < 500 cells/mm^3.
Known or suspected human immunodeficiency virus infected patients with a cluster of differentiation (CD4) cell count < 200 cells/mm3 or with a past or current acquired immunodeficiency syndrome (AIDS)-defining condition and unknown CD4 count.
A recent bone marrow transplant (in post-transplant hospital stay).
Receiving oral steroids > 20 mg prednisolone per day (or equivalent) or receiving immunosuppressant drugs after organ transplantation.
Receiving an antipyretic drug on a daily basis (eg., daily use of naproxen) whose regimen could not be modified during the first 3 days of study drug therapy.
A rapidly fatal illness, not expected to survive for 3 months.

6.2.2.2 cSSSI Trial VER001-9

The study population included patients with complicated SSSI defined as infection which met the following criteria:

- Suspected to be caused by only Gram-positive bacterial pathogens, including methicillin-resistant *S. aureus* (MRSA)
- Involving deeper soft tissue or requiring significant surgical intervention (such as major abscesses, burns on ⩽20% body
- surface area, traumatic wound infection, extensive/ulcerating cellulitis, and surgical wound infections)
- Accompanied by at least two of the following symptoms:
  - Drainage/discharge
  - Erythema
  - Fluctuance
  - Heat/localized warmth
  - Pain/tenderness to palpation
  - Swelling/induration

- Accompanied by at least one of the following systemic signs of infection or other complicating factor
  - Increased temperature (≥100.5° F [≥38.1° C] measured orally or its equivalent by a different method)
  - Increased WBC (>10/000/mm3)
  - Bandemia (>10% bands regardless of the total peripheral white count)
  - Other complicating factor, as determined by the investigator

Patients known or suspected to have osteomyelitis or septic arthritis, those with infections expected to need more than two surgical interventions during the study, and those with concomitant conditions requiring antimicrobial therapy that would interfere with the evaluability of the condition under study were excluded from participation.

6.2.3 Choice of Comparators

For the 3 SSSI efficacy trials, comparators were selected based on their use as standards of care in general clinical practice, as well as with concurrence by regulatory authorities in the US and EU.

6.2.3.1 Pivotal Phase 3 ABSSSI Studies (DUR001-301 and DUR001-302)

The 2 ABSSSI studies were of identical trial design (multicenter/multinational, randomized, double-blind, double-dummy), including the choice of comparator regimen (IV vancomycin q12h), with possible switch to oral linezolid 600 mg q12h after at least 3 days, provided the patient met the protocol-defined criteria for clinical improvement.

The dose of IV vancomycin was 1000 mg or 15 mg/kg (depending on the study site standard of care) q12h for 3 days (6 doses) to 14 days. A subject with impaired renal function had doses and intervals of vancomycin treatment adjusted by an unblinded pharmacist as necessary based on local standard of care. Subjects in the vancomycin group also received 30-minute placebo infusions on Days 1 and 8 to match the dalbavancin dosing regimen. In addition, investigators had the option of switching subjects in the comparator regimen from IV vancomycin to oral linezolid 600 mg administered q12h provided that the criteria for a switch to oral therapy were met. For the dalbavancin patients, a corresponding switch from placebo IV to oral placebo capsules was implemented to maintain the blind. The duration of treatment was 10 - 15 calendar days.

Systemic aztreonam and/or IV or oral metronidazole could be added to either treatment group if there was knowledge or suspicion of a mixed infection. Gram-negative or anaerobic therapy could be discontinued if culture results were negative at the discretion of the investigator.

6.2.3.2 Additional Phase 3 cSSSI Study VER001-9 Relevant to the Claimed Indication

The comparator in this study was IV linezolid 600 mg q12h, with a possible switch to oral linezolid 600 mg q12h, for a total course of therapy of 14 days. For blinding purposes, all subjects received IV infusions of placebo at the times required by the opposite treatment. All subjects initiated treatment intravenously, with the potential to switch to oral therapy 24

hours later (oral placebo or oral linezolid) for the remainder of the 14 day treatment period, providing that the criteria for a switch to oral therapy were met. Aztreonam IV and/or metronidazole (IV or oral) could be added as empirical treatment for mixed infections.

6.3 Criteria for Evaluation of Efficacy

As recommended in the 2010 draft FDA Guidance, and consistent with the 2 SPA agreements, clinical evaluation during treatment of the ABSSSI (the "on treatment" assessment) occurred on Day 3, 4, or 5 (phase 3 clinical trials only). Within 1–3 calendar days following the completion of study drug dosing (regardless of the day of completion), the EOT clinical and microbiological assessments of the SSSI occurred, and within 12 to 16 calendar days following the completion of study drug dosing, the TOC or SFU (short-term follow up) assessment (clinical and microbiological) occurred. In all phase 3 studies, subjects with a successful clinical response at TOC were contacted for a Late Follow-Up (LFU) assessment, on Day 70 (60-88) for DUR001-301 and DUR001-302; and on Day 39 (±3 days) n VER001-9, from start of study.

6.3.1 Primary Efficacy Outcomes

In Study DUR001-301 and Study DUR001-302, the primary efficacy variable measure was clinical response at 48-72 hours (± 3 hours, ie, 45-75 hours) post-study drug initiation in the ITT population. Clinical Responders were defined as patients whose lesions at 48-72 hours after the initiation of therapy had no increase in area, length, or width relative to baseline; and who had temperature consistently ≤ 37.6° C upon repeated measurement.

In Study VER001-9, the primary efficacy variable was clinical response in the CE population at TOC (Day 28), which was consistent with FDA Guidances in place in 2002-2003.

6.3.2 Secondary Efficacy Outcomes

In Study DUR001-301 and Study DUR001-302, the secondary outcome measure was clinical status at the EOT visit (Day 14) in the ITT and CE-EOT populations. Clinical status was also determined at the SFU visit.

A patient was programmatically defined as a clinical success based on the following:

- The patient's lesion size, as defined by erythema, had decreased from Baseline;
- The patient's temperature was ≤ 37.6^{o} C (by any measurement method).
- Local signs of fluctuance and localized heat/warmth were absent;
- Local signs of tenderness to palpation and swelling/induration were no worse than mild; and
- For patients with a wound infection, the severity of purulent drainage was improved and no worse than mild relative to Baseline.

A patient was defined as a clinical failure if at least 1 of the following criteria was met:

- The patient's lesion size as defined by erythema, was not decreased from Baseline
- Local signs of fluctuance and localized heat/warmth had not resolved
- Local signs of tenderness to palpation and swelling/induration were worse than mild
- For patients with a wound infection, the severity of the purulent drainage was the same or worsened relative to Baseline or was worse than mild
- The patient had a temperature of > 37.6^{o} C (by any measurement method) at the visit
- The patient received a new non-study systemic antibacterial treatment for the ABSSSI at any time from the first dose of study drug through the visit
- The patient died during the study period up to the visit
- Unless preplanned as part of non-drug therapy for the ABSSSI, the patient required surgical intervention more than 72 hours after the start of therapy for treatment of the ABSSSI under study
- The patient received study therapy for the ABSSSI under study beyond the protocol treatment period as a result of the investigator's assessment that additional drug therapy was needed for treatment of the underlying skin infection.

Patients were defined to have an indeterminate outcome if any data needed to determine whether the outcome was success or failure were missing. For example, if the assessment of the local signs was not completed at EOT, the patient was considered an indeterminate response for the analysis at EOT. By definition, patients with an indeterminate response were included in the denominator for analyses in the ITT and microITT populations (Section 6.5.1), and were counted as failures.

Additional secondary efficacy variable measures included investigator assessment of clinical response at EOT and SFU, per-patient microbiological efficacy, clinical efficacy by individual pathogens, and pathogen eradication rates for individual pathogens.

6.4 Results from the Phase 2/3 SSSI Studies

6.4.1 Patient Baseline Characteristics

Overall, the patients enrolled in the dalbavancin clinical program were representative of those in the intended clinical population (Weigelt 2005).

6.4.1.1 Demographic Characteristics

The demographic and Baseline characteristics were similar between dalbavancin and comparator groups in the phase 2/3 integrated analysis set (Table 34). All treatment groups included approximately equal proportions of male and female patients, and the majority of patients were White and < 65 years of age. The mean ages between dalbavancin and comparator groups were similar (48.3 vs. 49.2 years) and the mean proportion of patients that were ≥ 65 years of age was approximately 18%. The mean BMI between dalbavancin and comparator groups were similar (29.9 vs. 29.4 kg/m^2). Demographic and Baseline characteristics were similar in the ABSSSI population.

Table 34 Demographic and Other Characteristics of Phase 2/3 Patients

	Overall Phase 2/3[a] Population		ABSSSI Population[b]	
	Dalbavancin n = 1778	**Comparator n = 1224**	**Dalbavancin n = 652**	**Comparator n = 651**
Age (years): Mean (SD) Median Minimum–Maximum	48.3 (16.4) 47.0 16–93	49.2 (16.5) 49.0 18–92	48.9 (16.0) 49.0 18-85	50.3 (15.7) 51.0 18 - 84
Age distribution, n (%): < 65 years ≥ 65 years	 1465 (82.4) 313 (17.6)	 995 (81.3) 229 (18.7)	 546 (83.7) 106 (16.3)	 527 (81.0) 124 (19.0)
Gender, n (%): Male Female	 1066 (60.0) 712 (40.0)	 711 (58.1) 513 (41.9)	 388 (59.5) 264 (40.5)	 374 (57.5) 277 (42.5)
Race / Ethnicity, n (%): White Black Asian Hispanic/Latino Other	 1388 (78.1) 143 (8.0) 36 (2.0) ND 211 (11.9)	 1008 (82.4) 88 (7.2) 41 (3.3) ND 87 (7.1)	 587 (90.0) 28 (4.3) 27 (4.1) ND 10 (1.5)	 578 (88.8) 35 (5.4) 32 (4.9) ND 6 (0.9)
BMI (kg/m^2): N Mean (SD) Median Minimum – Maximum	 1761 29.9 (8.2) 27.9 14–98	 1218 29.4 (8.0) 27.8 14–91	 652 29.2 (7.17) 27.5 14 - 69	 650 29.1 (7.16) 27.6 17 - 65
BMI distribution, n (%): < 18.5 kg/m^2 18.5 to < 25 kg/m^2 ≥ 25 kg/m^2 Unknown	 23 (1.3) 465 (26.2) 1273 (71.6) 17 (1.0)	 18 (1.5) 359 (29.3) 841 (68.7) 6 (0.5)	 5 (0.8) 177 (27.1) 470 (72.1) 0 (0.0)	 9 (1.4) 203 (31.2) 438 (67.3) 1 (0.2)
Indication, n (%): cSSSI uSSSI CRBSI ABSSSI	 642 (36.1) 444 (25.0) 40 (2.2) 652 (36.7)	 322 (26.3) 217 (17.7) 34 (2.8) 651 (53.2)	 -- -- -- 652 (100)	 -- -- -- 651 (100)
Location, n (%): North America Western Europe Eastern Europe, ROW[c] Asia-Pacific	 1143 (64.3) 216 (12.1) 395 (22.2) 24 (1.3)	 689 (56.3) 118 (9.6) 389 (31.8) 28 (2.3)	 233 (35.7) -- 395 (60.6) 24 (3.7)	 234 (35.9) -- 389 (59.8) 28 (4.3)

[a] Includes data from the safety populations of Studies VER001-9, VER001-16, DUR001-301, and DUR001-302 (ABSSSI/cSSSI); VER001-5 (SSSI); VER001-8 (uSSSI); and VER001-4 (CRBSI)
[b] Includes data from the safety population of Studies DUR001-301 and DUR001-302 (ABSSSI)
[c] Rest of the World (excluding North America, Europe, and Asia-Pacific)

Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; CRBSI = catheter-related blood stream infections, ROW = Rest of World (excluding North America, Europe, and Asia-Pacific)

The demographics of the patients with ABSSSI were very similar to those of the overall phase 2/3 population. More patients were enrolled from North America in Study VER001-9 than in the ABSSSI studies or included in the overall phase 2/3 population (data not shown).

6.4.1.2 Comorbidities at Baseline

In the 3 phase 3 studies relevant to the proposed (DUR001-301, DUR001-302 and VER001-9), a substantial percentage of patients had diabetes mellitus (ranging from 9.4% to 36.7% across treatment groups). The prevalence of patients with a history of diabetes mellitus was higher in the patients with cSSSI (Study VER001-9) compared to patients with ABSSSI (Study DUR001-301 and Study DUR001-302); however, the proportion of patients with fasting blood glucose measurements, diagnostic of either pre-diabetes or diabetes mellitus, in these studies was notable (40.3% in DUR001-301 and 38.0% in DUR001-302, respectively) and consistent with other epidemiologic studies (Cowie 2009). The percentage of patients with vascular disease ranged from 6.4% to 20.4% across treatment groups. In Study VER001-9 a significantly higher percentage of patients in the dalbavancin group than the linezolid group presented with vascular disease (10.7% vs. 6.4%; p=0.044).

6.4.2 Disease Categories

In Study DUR001-301, the most common types of infection were cellulitis (52.9%), major abscess (27.6%), and wound infection (19.5%). Similarly, in Study DUR001-302 the most common types of infection were cellulitis (54.1%), major abscess (24.0%), and wound infection (21.8%). For patients with cSSSI in Study VER001-9, the most common types of infection were major abscess (32.3%), cellulitis (28.2%), and other deep soft tissue infection (16.6%).

6.4.3 Distribution of Baseline Pathogens

Baseline pathogens in the microbiological ITT (MicroITT) population are tabulated by study and treatment group in Table 35.

The most prevalent pathogens isolated in these studies were in accordance with the documented epidemiology of SSSIs from recent surveillance studies (Jones 2003; Bell 2002; Diekema 2001; Fluit 2001a; Jones1999; Rennie2003). As expected, in all 7 studies of infection in the Phase 2/3 program, *S. aureus* was the most common Gram-positive pathogen, isolated from 73.8% of patients with a pathogen overall (1438/1949 patients). Other common pathogens included *S. pyogenes*, *S. agalactiae*, *Streptococcus* Group G and viridans Group streptococci.

The prevalence of MRSA was influenced in part by the study design, and in part by the sub-type of infection and geographic locations of enrolled patients, and ranged from 17.5% in Study DUR001-302 to 45.9% in Study VER001-9. The prevalence of MRSA was 69.4% in Study VER001-16, which was designed to enrich for MRSA.

Table 35 Baseline Pathogens in Microbiological ITT Populations, (Phase 2/3 Studies)

		Dalbavancin					Comparator					Total				
		All	*S. aureus*		MRSA		All	*S. aureus*		MRSA		All	*S. aureus*		MRSA	
Study	Indication	Isolates	n	(%)	n	(%)	Isolates	n	(%)	n	(%)	Isolates	n	(%)	n	(%)
Pivotal Phase 3 Studies																
DUR001-301	ABSSSI	166	122	(73.5)	44	(26.5)	175	128	(73.1)	39	(22.3)	334	250	(74.9)	83	(24.9)
DUR001-302	ABSSSI	209	135	(64.6)	46	(22.0)	199	129	(64.8)	28	(14.1)	423	264	(62.4)	74	(17.5)
Supportive Phase 2/3 Study Relevant to the Claimed Indication																
VER001-9	cSSSI	391	318	(81.3)	181	(46.3)	215	174	(80.9)	97	(45.1)	606	492	(81.2)	278	(45.9)
Other Supportive Phase 2/3 Studies																
VER001-4	CRBSI	26	11	(42.3)	5	(19.2)	28	12	(42.9)	9	(32.1)	54	23	(42.6)	14	(25.9)
VER001-5	cSSSI	32	24	(75.0)	11	(34.4)	17	10	(58.8)	2	(11.8)	49	34	(69.4)	13	(26.5)
VER001-8	uSSSI	260	189	(72.7)	51	(19.6)	112	86	(76.8)	17	(15.2)	372	275	(73.9)	68	(18.3)
VER001-16	uSSSI/ cSSSI	76	69	(90.8)	55	(72.4)	35	31	(88.6)	22	(62.9)	111	100	(90.1)	77	(69.4)
All Studies	**All**	**1160**	**868**	**(74.8)**	**393**	**(33.9)**	**781**	**570**	**(73.0)**	**214**	**(27.4)**	**1949**	**1438**	**(73.8)**	**607**	**(31.1)**

Abbreviations: ABSSSI= acute bacterial skin and skin structure infections; cSSSI=complicated skin and skin structure infection; MRSA= methicillin resistant *Staphylococcus aureus*; uSSSI=uncomplicated skin and skin structure infection.

6.5 Statistical Methodology

6.5.1 Analysis Populations

In the 2 studies designed to evaluate the efficacy of dalbavancin in ABSSSI, the following main patient populations were identified for the efficacy analyses:

- ITT Population:
  - All randomized patients regardless of whether or not they received study drug.
- Safety Population:
  - All patients in the ITT population who received at least 1 dose of dalbavancin or active comparator study drug.
- Microbiological ITT (MicroITT) Population:
  - All patients in the ITT population with at least 1 Gram-positive pathogen identified at Baseline.
- Clinically Evaluable (CE) Population:
  - Patients with an ABSSSI (Study DUR001-301 and Study DUR001-302) at Baseline who did not violate the protocol in such a way that precluded clinical evaluability. The specific protocol violations leading to exclusion from the CE population are defined in each of the clinical study reports. A CE population was identified for each visit, ie, end-of-therapy (EOT) visit and short-term follow-up (SFU) visit.
- Microbiologically Evaluable (ME) Population:
  - Met all the criteria for the CE population and had a Gram-positive causative pathogen at Baseline. An ME population was identified for each visit (EOT, SFU, TOC).

Clinical evaluation and treatment of the ABSSSI (the "on treatment" assessment) occurred on Study Day 2, Day 3, Day 4, and Day 8 (Study DUR001-301 and Study DUR001-302). Within 2 to 3 calendar days following the completion of study medication dosing (regardless of the day of completion), the EOT clinical and microbiological assessments of the SSSI occurred, and within 12 to 16 calendar days following the completion of study medication dosing, the SFU assessments occurred in DUR001-301 and DUR001-302.

In the 2 pivotal phase 3 studies, patients with a successful clinical response at SFU/TOC were contacted for a Late Follow-Up (LFU) assessment on or around Day 70.

In general, the percentages of patients included in the MicroITT population and the CE and ME populations were well-balanced across treatment groups within a study.

6.5.2 Non-inferiority Margin Justification

In the phase 3 Studies DUR001-301 and DUR001-302, the primary efficacy parameter was the clinical response rate at 48 to 72 hours (±3 hours [ie, 45-75 hours]) post-study drug initiation in the ITT population, defined as cessation of spread of the erythema of the lesion and absence of fever, as justified in FDA draft guidance (August 2010).

The observed difference in percentage of responders at 48 to 72 hours (dalbavancin treatment group minus the vancomycin/linezolid treatment group) was determined and a 95% confidence interval (CI) for the observed difference was computed with stratification (for the presence or absence of fever at Baseline). If the lower limit of the 2-sided 95% CI for the difference in response rates in the ITT population was greater than -10%, the non-inferiority of dalbavancin to vancomycin/linezolid was concluded.

The non-inferiority margin, or "delta" of 10.0 percentage points selected for studies DUR001-301 and DUR001-302 was based on ICH E10 Guidance (2000) and agreed at the time with the FDA and, as appropriate, included a consideration of the clinical severity of the infection under study and the attendant risk to patients if a truly inferior new drug were approved for use.

Assay sensitivity in a non-inferiority trial requires that the control drug is effective relative to the standard of care so that the study will not inappropriately conclude that an ineffective new drug is non-inferior, and therefore potentially approvable (Hwang, 1999; Temple 2000). For the recently defined ABSSSI and the cSSSI indications (particularly those infections sufficiently severe to require parenteral treatment), antibiotic therapy is accepted as a critical intervention, and the comparator agents used were well-established as adequate to exert the intended effect. Therefore, the pivotal phase 3 trials most certainly had adequate assay sensitivities.

Where applicable, secondary efficacy variables were analyzed using the same methodology as for the primary endpoint. However, it should be noted that the studies were not intended to demonstrate non-inferiority for secondary efficacy variables, although Studies DUR001-301 and DUR001-302 were adequately powered to do so.

The primary endpoint (clinical response rate in the ITT population at 48 to 72 hours [±3 hours], ie, 45-75 hours) post-study drug initiation in Studies DUR001-301 and DUR001-302 was the sole endpoint for confirmatory statistical testing. All other endpoints, populations, and time points were considered secondary and supportive. Therefore, no adjustments for multiple endpoints were necessary. When applicable, other efficacy variables were analyzed using the same methodology as for the primary endpoint.

6.5.3 Sample Size Justification

Sample size determinations were based on assumptions regarding the ITT population in Studies DUR001-301 and DUR001-302. Nonetheless, efficacy analyses were conducted in several populations, including the ITT, CE, SFU, MicroITT, and ME populations. All analyses were pre-specified in a SAP, except in the few instances in which post-hoc analyses are specifically noted in the study reports. In addition to assumptions regarding the rate for the primary outcome measure and a one-sided alpha of 0.025, an NI margin of -10% and a 90% power were assumed.

6.6 Results of Individual Phase 3 Studies Pivotal to the ABSSSI Indication

6.6.1 Study DUR001-301

In Study DUR001-301, a total of 573 patients from North America and Eastern Europe were randomized to the study with a 1:1 randomization of dalbavancin (288) to vancomycin/-linezolid (285). A total of 568 patients (284 dalbavancin, 284 vancomycin/linezolid) received at least 1 dose of study medication. The dalbavancin and vancomycin/linezolid groups were well-matched with respect to demographic and Baseline characteristics.

6.6.1.1 Baseline Pathogens

In this study, 153/284 (53.9%) of dalbavancin-treated patients and 155/284 (54.6%) of vancomycin/linezolid-treated patients had a Baseline pathogen isolated. The most common Baseline pathogen was *S. aureus* (isolated from 74.9% of patients with a Baseline pathogen). Of the *S. aureus* isolates, 33.2% were MRSA.

6.6.1.2 Primary Efficacy Variable

The prospectively-defined margin of non-inferiority for this study was -10.0%. For the primary efficacy analysis of clinical response in the ITT population at 48 to 72 hours (±3 hours, ie, 45-75 hours) post-study drug initiation, dalbavancin was non-inferior to vancomycin/linezolid (83.3% versus 81.8%; difference 1.5; 95% CI -4.6%, 7.9%).

SENSITIVITY ANALYSES OF THE PRIMARY EFFICACY VARIABLE

Thirteen separate pre-specified sensitivity analyses of the primary efficacy analysis were performed (Table 36). Overall, results of all of the sensitivity analyses were consistent with results of the primary efficacy analysis, with the treatment difference ranging between -0.2% and 3.3%, and the lower limit of the 95% CI for the treatment difference exceeding -10% in each case.

Table 36. Sensitivity Analyses on the Primary Efficacy Variable: of Clinical Response at 48 to 72 Hours (ITT Population)

Number	Sensitivity Analysis
1	Confidence intervals are calculated using Miettinen and Nurminen method without adjustments.
2	Each patient randomized using incorrect fever stratum is moved, in the analysis, to the correct stratum.
3	Patients with insufficient data at 48-72 hours to determine whether the patient is a responder or non-responder are considered as responders
4	Three sequential temperature measurements are utilized to determine response regardless of whether these are 3-9 hours apart (but no more than 12 hours apart).
5	Only the first temperature measurement taken 48-72 hours after first dose of study drug is utilized.
6	The observation window for the three sequential temperature measurements is extended such that the first of three consecutive measurements below 37.6°C occurs as late as 72 hours after the first dose of study drug.
7	Only one temperature measurement is required within 24 hours of the first measurement taken 48-72 hours after the first dose of study drug.
8	Exclude temperature from the primary outcome measure for success and failure, and define success as at least a 20% decrease from Baseline in lesion (length × width only).
9	Patients are defined as non-responders if the decrease from Baseline in lesion size (length × width) is <10% at 48-72 hours and there was an increase in either the longest length or the widest width.
10	For patients missing lesion measurements at 48-72 hours, the last non-missing lesion measurement is carried forward and is used in the analysis.
11	Define success as no increase from Baseline in lesion area (length × width) and the patient is afebrile as defined in primary efficacy analysis.
12	Exclude temperature from the primary outcome measure and define success as no increase from Baseline in the lesion area (length × width)
13	Exclude lesion measurement from the primary outcome measure and define success based only on the temperature measurements as defined in primary efficacy analysis.

The sensitivity analysis that excluded temperature from the primary outcome measure and defined success as ≥ 20% decrease from Baseline in lesion area (length × width only) showed 259 (89.9%) dalbavancin-treated patients and 259 (90.9%) vancomycin/linezolid-treated patients as clinical responders. The difference in clinical response rates was -1.0 (95% CI, -5.7, 4.0).

6.6.1.3 Secondary Efficacy Analyses

Clinical success rates in the CE Population at EOT, which took place on Days 14 or 15, or within 3 days following premature discontinuation of treatment, were similar between patients in the dalbavancin (87.0%) and vancomycin/linezolid (91.4%) treatment regimens. The lower boundary of the adjusted 2-sided 95% CI around the treatment difference adjusted

for fever was -10.0%. In the ITT analysis, clinical success occurred in 81.9% of patients in the dalbavancin group and 86.7% of patients in the vancomycin/linezolid group, and the lower bound of the 95% CI adjusted for fever was -10.7%.

In order to address an imbalance in the numbers of indeterminate subjects, a multiple imputation analysis was performed on this ITT outcome, which resulted in an adjusted treatment difference of -3.3% and a lower limit of -9.1% (Table 37).

Table 37. Clinical Status at the End-of-Treatment Visit (ITT population) - Multiple Imputation Analysis

Study Population	Dalbavancin (N=288) n (%)	Vancomycin/linezolid (N=285) n (%)	Difference (95% CI)
Clinical status	236 (81.9%)	247 (86.7%)	-4.8 (-10.7, 1.3)
Clinical success - multiple imputation	236 (81.9%)	247 (86.7%)	-3.3% (-9.1, 2.5)
Indeterminate	14 (4.9%)	9 (3.2%)	

Abbreviations: CI = confidence interval; ITT = intent-to-treat

The study protocol had pre-specified a sensitivity analysis to assess clinical status at EOT, such that local signs of fluctuance or localized heat/warmth (if present at Baseline) had to be improved from Baseline for the patient outcome to be considered a success at EOT rather than completely resolved. Results of this sensitivity analysis showed similar rates of clinical success at EOT between the dalbavancin and vancomycin/linezolid groups in both the CE (93.5% vs 94.7%; 95% CI -5.4, 3.4, respectively) and ITT (87.8% vs 89.5%; 95% CI -6.9, 3.7, respectively) populations.

Clinical success rates at EOT based on investigator assessment was a key secondary analysis in the ABSSSI trials. To be classified as a clinical outcome of success at EOT based on investigator assessment, there was to be resolution or improvement of all signs and symptoms of the infection to such an extent that no further antibacterial treatment was given. An outcome of clinical failure in this analysis was assigned if any of the following criteria were met: (1) persistence of ≥1 local or systemic signs and symptoms of ABSSSI such that new systemic antibacterial treatment was given; (2) unplanned surgical intervention >72 hours after start of therapy for the treatment of ABSSSI; (3) TEAE leading to discontinuation of study drug, and patient required additional antibiotic therapy to treat the ABSSSI; (4) the patient received study therapy beyond the protocol treatment period as a result of the investigator's assessment that additional drug therapy is needed for treatment of the underlying skin infection; (5) death during the study period. Results for this analysis were also consistent with results of the sensitivity analyses in the CE (94.7% vs 97.5%; 95% CI -6.7, 0.7) and ITT (90.3% vs 91.9%; 95% CI -6.4, 3.1) populations.

High per-patient microbiological success rates were observed throughout the study at EOT in the ME (86.2% vs 89.1%) and MicroITT (79.1% vs 87.7%) populations.

At EOT in the MicroITT population, clinical success rates were similar in the two treatment groups among patients with monomicrobial infections at Baseline for those with *S. aureus* infection (including MRSA and methicillin-susceptible [MSSA]) and *S. pyogenes* infections. The numbers of patients with *S. agalactiae* and *S. anginosus* group monomicrobial infections at Baseline were low, but generally, the clinical success rates were similar between the dalbavancin and vancomycin/linezolid treatment groups. The proportion of patients with clinical status of success at early response, 48 to 72 hours, was similar to that at EOT. Overall, clinical success rates at EOT and at 48 to 72 hours were similar in groups of patients with monomicrobial infection and polymicrobial infection at Baseline.

6.6.2 Study DUR001-302

In Study DUR001-302, a total of 739 patients from North America, Europe, South Korea, Taiwan, South Africa, and Israel, were randomized to the study with a 1:1 randomization of dalbavancin (371) to vancomycin/linezolid (368). After review of a prespecified, blinded interim analysis and a slightly lower point estimate of efficacy than intitally assumed, a blinded Data Monitoring Committee recommended that the sample size be increased to 740 patients from the intitial sample size of 573. A total of 735 patients (368 dalbavancin, 367 vancomycin/-linezolid) received at least one dose of study medication. The dalbavancin and vancomycin groups were well matched with respect to demographic and Baseline characteristics. A total of 665 patients completed the study (332 patients and 333 patients in the dalbavancin and vancomycin/linezolid treatment groups, respectively).

6.6.2.1 Baseline Pathogens

In this study, 184/368 (50.0%) of dalbavancin-treated patients and 174/367 (47.4%) of vancomycin/linezolid-treated patients had a Baseline pathogen isolated. The most common Baseline pathogen was *S. aureus* (isolated from 263/335 (78.5%) of patients with a Baseline pathogen). Of the *S. aureus* isolates, 74/263 (28.1%) were MRSA.

6.6.2.2 Primary Efficacy Variable

The prospectively defined margin of non-inferiority for this study was -10.0%. For the primary efficacy analysis of clinical response in the ITT population at 48 to 72 hours (±3 hours, ie, 45-75 hours) post-study drug initiation, dalbavancin was non-inferior to vancomycin/linezolid (76.8% vs 78.3%; difference -1.5; 95% CI -7.4, 4.6).

SENSITIVITY ANALYSES OF THE PRIMARY EFFICACY VARIABLE

In a manner similar to the other ABSSSI study (Table 36, Section 6.6.1.2), thirteen separate prespecified sensitivity analyses of the primary efficacy analysis were performed. Overall, results of all of the sensitivity analyses were consistent with results of the primary efficacy analysis, with the treatment difference ranging between -1.7 and 2.8 and the lower limit of the 95% CI for the treatment difference always within the 10% NI margin.

The sensitivity analysis that excluded temperature from the primary outcome measure and defined success as ≥ 20% decrease from Baseline in lesion area (length x width only) showed 325 (87.6%) patients and 316 (85.9%) patients in the dalbavancin and vancomycin/linezolid

treatment groups, respectively, as clinical responders. The difference in clinical response rates was 1.7% (95% CI, -3.2, 6.7).

6.6.2.3 Secondary Efficacy Analyses

Clinical status in the CE-EOT population and ITT population at EOT (Day 14-15) and clinical status in the CE-SFU population and ITT population at SFU, analyzed as secondary efficacy endpoints, but for which 95% CIs are presented, supported the result of the primary analysis. At EOT in the CE-EOT population, clinical success occurred in 93.5% of subjects in the dalbavancin group and 92.7% of subjects in the vancomycin/linezolid group. The lower boundary of the adjusted 2-sided 95% CI around the treatment difference adjusted for fever was -3.3%. In the ITT analysis, clinical success occurred in 88.7% of subjects in the dalbavancin group and 85.6% of subjects in the vancomycin/linezolid group, and the lower bound of the 95% CI adjusted for fever was -1.8%.

As in the previous study, in order to address an imbalance in the numbers of indeterminate subjects, a multiple imputation analysis was performed on this ITT outcome, which resulted in an adjusted treatment difference of 0.6% and a lower limit of -3.9% (Table 38).

Table 38. Clinical Status of Success at End-of-Treatment (ITT Population) - Multiple Imputation Analysis

Study Population	Dalbavancin (N=371) n (%)	Vancomycin/Linezolid (N=368) n (%)	Difference (95% CI)
Clinical Status	329/371 (88.7%)	315/368 (85.6%)	3.1 (-1.8, 8.0)
Clinical Status - multiple imputation	329/371 (88.7%)	315/368 (85.6%)	0.6% (-3.9, 5.0)
Indeterminate	10	20	

Abbreviations: CI= confidence interval; ITT = intent-to-treat.

The study protocol had pre-specified a sensitivity analysis to assess clinical status at EOT, such that local signs of fluctuance or localized heat/warmth (if present at Baseline) had to be improved from Baseline for the patient outcome to be considered a success at EOT. Results of this sensitivity analysis showed similar rates of clinical success at EOT between the two treatment groups in both the CE (93.5% vs 95.0%; 95% CI -5.4, 2.2) and ITT (89.5% vs 87.5%; 95% CI -2.4, 6.8) populations.

Investigator-assessed clinical outcomes were consistent with results of the sensitivity analysis and were similar between treatment groups at EOT in both the CE (314/324 [96.9%] in dalbavancin treatment group and 290/302 [96.0%] in the vancomycin/linezolid treatment group) and ITT populations (342/371 [92.2%] in dalbavancin treatment group and 332/368 [90.2%] in the vancomycin/linezolid treatment group.

High per-patient microbiological success rates in the dalbavancin and vancomycin/linezolid treatment group were observed at EOT in the ME (95.5% vs 95.4%) and MicroITT (92.4% vs 86.8%) populations.

At EOT in the MicroITT population, the proportion of patients with monomicrobial infections at Baseline with a clinical status of success was similar in the two treatment groups for those with *S. aureus* infection (including MRSA and MSSA) and *S. pyogenes* infections. The numbers of patients with *S. agalactiae* and *S. anginosus* group monomicrobial infections at Baseline were low, but generally the clinical success rates were similar between the dalbavancin and vancomycin/linezolid treatment groups. The proportion of patients with clinical status of success at early response 48 to 72 hours was similar to EOT. Overall, clinical success rates at EOT and at 48 to 72 hours were similar in groups of patients with monomicrobial and polymicrobial infection at Baseline.

6.6.3 Additional Phase 3 Studies Relevant to the Claimed Indication

6.6.3.1 Study VER001-9 (cSSSI) (conducted 2003-2004)

In Study VER001-9, a total of 873 patients from North America and Europe were randomized to the study with a 2:1 randomization of dalbavancin (583) to linezolid (290). There were 854 patients (571 dalbavancin, 283 linezolid) who received at least one dose of study medication. The dalbavancin and vancomycin/linezolid groups were well matched with respect to demographic and Baseline characteristics.

BASELINE PATHOGENS

In this study, 358/571 (62.7%) of dalbavancin-treated patients and 192/283 (67.8%) of vancomycin/linezolid-treated patients had a Baseline pathogen isolated. The most common Baseline pathogen was *S. aureus* (isolated from 492/550 [89.5%] of patients with a Baseline pathogen). Of the *S. aureus* isolates, 278/492 (56.5%) were MRSA.

PRIMARY EFFICACY VARIABLE

In the analysis of the primary efficacy endpoint (clinical response at TOC in the CE population) in Study VER001-9, dalbavancin demonstrated comparable clinical efficacy to linezolid (88.9% for dalbavancin, 91.2% for linezolid) and met the requirement of statistical demonstration of non-inferiority. The treatment difference between the two treatment groups was -2.21% with a 95% CI of -7.28% to 2.86%.

6.6.4 Other Supportive Phase 2/3 Studies

6.6.4.1 Study VER001-16 – cSSSI and uSSSI (conducted 2003-2004)

In Study VER001-16, a total of 160 patients from North America were randomized to the study with a 2:1 randomization (dalbavancin: vancomycin). There were 156 patients (107 dalbavancin, 49 vancomycin) who received at least one dose of study medication. The dalbavancin and vancomycin groups were well matched with respect to demographic and Baseline characteristics.

BASELINE PATHOGENS

In this study, 71/107 (66.4%) of dalbavancin-treated patients and 33/49 (67.3%) of vancomycin-treated patients had a Baseline pathogen isolated. The most common Baseline

pathogen was *S. aureus* (isolated from 90.1% of patients with a Baseline pathogen). Of the *S. aureus* isolates, 77/100 (77.0%) were MRSA.

PRIMARY EFFICACY VARIABLE

The prospectively defined margin of non-inferiority for this study was 20%. For the primary efficacy analysis of clinical response in the CE population at TOC, dalbavancin was at least as effective as vancomycin (89.9% vs 86.7% 95% CI -13.0%, 19.4%]).

6.6.4.2 Study VER001-5 – cSSSI (conducted 2001-2002)

In Study VER001-5, a total of 62 patients were randomized to the study with a 2:1 randomization (dalbavancin: standard antibiotic therapy, as defined by investigator prior to randomization). All 62 patients (41 dalbavancin, 21 comparator) received at least one dose of study medication. The dalbavancin and comparator groups were generally well-matched with respect to demographic and Baseline characteristics. Twenty patients in the dalbavancin group received 7 days of dalbavancin (1 dose) and 20 patients received 14 days of dalbavancin (2 doses). The percentage of patients who received 7 versus 14 days of therapy in the comparator group was similar.

BASELINE PATHOGENS

There were 27/41 (65.9%) of dalbavancin-treated patients and 14/21 (66.7%) of comparator-treated patients with a Baseline pathogen. The majority of patients in the MicroITT population presented with SSSI that involved a single Gram-positive Baseline pathogen, the most common of which was *S. aureus* (69.4% of all Gram-positive Baseline isolates). MRSA was isolated from Baseline cultures of 34.4% and 11.8% of patients in the dalbavancin and comparator groups, respectively.

PRIMARY EFFICACY VARIABLE

In the analysis of the primary endpoint, clinical response at follow-up (14 days after EOT; equivalent to TOC in other studies) in the CE population was dose dependent in the dalbavancin patients, ie 61.5% in those treated with one dose, and 94.1% in those treated with 2 doses. The clinical success rate in the comparator arm was 76.2%.

6.6.4.3 Study VER001-8 – uSSSI (conducted 2002-2004)

In Study VER001-8, a total of 553 patients were randomized to the study with a 2:1 randomization (dalbavancin: cefazolin). All 553 patients (367 dalbavancin, 186 cefazolin) received at least one dose of study medication. The dalbavancin and cefazolin groups were generally well-matched with respect to demographic and Baseline characteristics. The majority of patients in the dalbavancin group (273 patients, 74.4%) received 7 days of dalbavancin (1 dose) and 94 patients (25.6%) received 14 days of dalbavancin (2 doses). The percentage of patients who received 7 versus 14 days of therapy in the comparator group was similar. A total of 219 (39.6%) patients enrolled in Europe, and 334 (60.4%) enrolled in North America.

BASELINE PATHOGENS

There were 224/367 (61.0%) of dalbavancin-treated patients and 98/186 (52.7%) of cefazolin-treated patients with a Baseline pathogen. The majority of patients in the MicroITT population presented with SSSI that involved a single Gram-positive Baseline pathogen, the most common of which was *S. aureus* (73.9% of all Gram-positive Baseline isolates). Although patients known or suspected to have SSSI involving MRSA were to be excluded from the study and sites were chosen specifically based on low local MRSA rates, MRSA was isolated from Baseline cultures of 19.6% and 15.2% of patients in the dalbavancin and cefazolin groups, respectively.

PRIMARY EFFICACY VARIABLE

In the analysis of the primary endpoint, clinical response at TOC in the CE population, dalbavancin and cefazolin demonstrated identical point estimates of clinical success (89.1%). Clinical response in the ITT population was similar between treatment groups.

6.6.5 Other Studies

6.6.5.1 Study VER001-4 – Catheter-Related Blood Stream Infections (CRBSI) (conducted 2002-2003)

In Study VER001-4, a total of 75 patients were randomized to the study. Of the 41 patients randomized to dalbavancin 33 received a weekly dose and 7 a daily dose of study medication. One patient randomized to dalbavancin was not treated. The 34 patients randomized to comparator received vancomycin. The dalbavancin and comparator groups were generally well-matched with respect to demographic and Baseline characteristics. The daily dalbavancin treatment group was eventually removed from the study and not analyzed for efficacy, based on the establishment of the preferred weekly regimen in other Phase 2 protocols.

PRIMARY EFFICACY VARIABLE

There were 25/40 (62.5%) of dalbavancin-treated patients and 28/34 (82.4%) of comparator-treated patients with a Baseline pathogen. The majority of patients in the MicroITT population presented with CRBSI, the most common of which was *S. aureus* (42.6% of all Baseline isolates). MRSA was isolated from Baseline cultures of 19.2% and 25.9% of patients in the dalbavancin and comparator groups, respectively.

In the primary efficacy analysis, overall response in the MicroITT population at TOC, patients who received weekly dalbavancin had a higher success rate (87.0%, 95% CI: 73.2%, 100.0%) than patients who received vancomycin (50.0%, 95% CI: 31.5%, 68.5%).

6.7 Analysis of Key Efficacy Results across Pivotal Phase 3 Studies

In this section, efficacy is reviewed from the perspective of the 2 ABSSSI studies, DUR001-301 and DUR001-302.

6.7.1 Clinical Outcomes across Pivotal Studies

The clinical program to evaluate the efficacy of IV dalbavancin for the treatment of ABSSSIs caused by Gram-positive bacteria comprised 2 phase 3 studies. Table 39 compares primary and key secondary clinical outcomes by study population between the 2 pivotal phase 3 ABSSSI studies.

Table 39 Clinical Outcomes, Phase 3 ABSSSI Studies DUR001-301 and DUR001-302 by Study Population

	DUR001-301		DUR001-302		Pooled DUR001-301 and DUR001-302			
	Dalbavancin	Comparator	Dalbavancin	Comparator	Dalbavancin	Comparator	Treatment Difference	95% CI
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
ITT, N1	**N=288**	**N=285**	**N=371**	**N=368**	**N=659**	**N=653**		
Early Clinical Response at 48 to 72 Hours								
Responder	240 (83.3)	233 (81.8)	285 (76.8)	288 (78.3)	525 (79.7)	521 (79.8)	-0.1	-4.5, 4.2
Nonresponder	48 (16.7)	52 (18.2)	86 (23.2)	80 (21.7)	134 (20.3)	132 (20.2)		
≥ 20% Reduction in Lesion Area from Baseline								
Responder	259 (89.9)	259 (90.9)	325 (87.6)	316 (85.9)	584 (88.6)	575 (88.1)	0.6	-2.9, 4.1
Nonresponder	29 (10.1)	26 (9.1)	46 (12.4)	52 (14.1)	75 (11.4)	78 (11.9)		
Clinical Status at EOT								
Success	236 (81.9)	247 (86.7)	329 (88.7)	315 (85.6)	565 (85.7)	562 (86.1)	-0.3	-4.1, 3.5
Failure	38 (13.2)	29 (10.2)	32 (8.6)	33 (9.0)	70 (10.6)	62 (9.5)		
Indeterminate [a]	14 (4.9)	9 (3.2)	10 (2.7)	20 (5.4)	24 (3.6)	29 (4.4)		
Clinical Status at SFU								
Success	241 (83.7)	251 (88.1)	327 (88.1)	311 (84.5)	568 (86.2)	562 (86.1)	0.1	-3.6, 3.9
Failure	18 (6.3)	13 (4.6)	18 (4.9)	23 (6.3)	36 (5.5)	36 (5.5)		
Indeterminate[a]	29 (10.1)	21 (7.4)	26 (7.0)	34 (9.2)	55 (8.3)	55 (8.4)		
Investigator Assessment of Clinical Response at EOT								
Success	260 (90.3)	262 (91.9)	342 (92.2)	332 (90.2)	602 (91.4)	594 (91.0)	0.4	-2.7, 3.5
Failure	16 (5.6)	9 (3.2)	16 (4.3)	19 (5.2)	32 (4.9)	28 (4.3)		
Indeterminate[a]	12 (4.2)	14 (4.9)	13 (3.5)	17 (4.6)	25 (3.8)	31 (4.7)		

Table 39 Clinical Outcomes, Phase 3 ABSSSI Studies DUR001-301 and DUR001-302 by Study Population

	DUR001-301		DUR001-302		Pooled DUR001-301 and DUR001-302			
	Dalbavancin	Comparator	Dalbavancin	Comparator	Dalbavancin	Comparator	Treatment Difference	95% CI
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
ITT, N1	**N=288**	**N=285**	**N=371**	**N=368**	**N=659**	**N=653**		
Investigator Assessment of Clinical Response at SFU								
Success	248 (86.1)	255 (89.5)	326 (87.9)	317 (86.1)	574 (87.1)	572 (87.6)	-0.5	-4.1, 3.1
Failure	17 (5.9)	10 (3.5)	18 (4.9)	20 (5.4)	35 (5.3)	30 (4.6)		
Indeterminate[a]	23 (8.0)	20 (7.0)	27 (7.3)	31 (8.4)	50 (7.6)	51 (7.8)		
CE-EOT, N2	**246**	**243**	**324**	**302**	**570**	**545**		
Clinical Status								
Success	214 (87.0)	222 (91.4)	303 (93.5)	280 (92.7)	517 (90.7)	502 (92.1)	-1.5	-4.8, 1.9
Failure	32 (13.0)	21 (8.6)	21 (6.5)	22 (7.3)	53 (9.3)	43 (7.9)		
Sensitivity Analysis - Clinical Status								
Success	230 (93.5)	230 (94.7)	303 (93.5)	287 (95.0)	533 (93.5)	517 (94.9)	-1.4	-4.2, 1.4
Failure	15 (6.1)	9 (3.7)	19 (5.9)	15 (5.0)	34 (6.0)	24 (4.4)		
Indeterminate[a]	1 (0.4)	4 (1.6)	2 (0.6)	0 (0.0)	3 (0.5)	4 (0.7)		
Investigator Assessment of Clinical Response								
Success	233 (94.7)	237 (97.5)	314 (96.9)	290 (96.0)	547 (96.0)	527 (96.7)	-0.7	-3.0, 1.5
Failure	12 (4.9)	4 (1.6)	10 (3.1)	12 (4.0)	22 (3.9)	16 (2.9)		
Indeterminate[a]	1 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)		
CE-SFU, N3	**226**	**229**	**294**	**272**	**520**	**501**		
Clinical Status								
Success	212 (93.8)	220 (96.1)	283 (96.3)	257 (94.5)	495 (95.2)	477 (95.2)	-0.0	-2.7, 2.7
Failure	14 (6.2)	9 (3.9)	11 (3.7)	15 (5.5)	25 (4.8)	24 (4.8)		

Table 39 Clinical Outcomes, Phase 3 ABSSSI Studies DUR001-301 and DUR001-302 by Study Population

	DUR001-301		DUR001-302		Pooled DUR001-301 and DUR001-302			
	Dalbavancin	Comparator	Dalbavancin	Comparator	Dalbavancin	Comparator	Treatment Difference	95% CI
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
ITT, N1	**N=288**	**N=285**	**N=371**	**N=368**	**N=659**	**N=653**		
Sensitivity Analysis - Clinical Status								
Success	212 (93.8)	217 (94.8)	284 (96.6)	258 (94.9)	496 (95.4)	475 (94.8)	0.5	-2.2, 3.3
Failure	12 (5.3)	9 (3.9)	10 (3.4)	14 (5.1)	22 (4.2)	23 (4.6)		
Indeterminate[a]	2 (0.9)	3 (1.3)	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.6)		
Investigator Assessment of Clinical Response								
Success	213 (94.2)	223 (97.4)	280 (95.2)	258 (94.9)	493 (94.8)	481 (96.0)	-1.2	-3.9, 1.5
Failure	13 (5.8)	5 (2.2)	12 (4.1)	12 (4.4)	25 (4.8)	17 (3.4)		
Indeterminate[a]	0 (0.0)	1 (0.4)	2 (0.7)	2 (0.7)	2 (0.4)	3 (0.6)		

[a] Indeterminate was a subset of the response of 'Failure," if any data used to determine clinical success or failure were missing.

Notes: Percentages are calculated as 100 x (n/N1, N2, or N3). Treatment difference is the weighted (by study) difference in response/success rates between the dalbavancin and vancomycin/linezolid treatment groups. 95% CI (Confidence Interval) is determined using the weighted method by Miettinen and Nurminen.

Abbreviations: EOT = End of Treatment; ISE = Integrated Summary of Efficacy; ITT = Intent to Treat; n = Number of patients in the specific category; N1 = Number of patients in the intent to treat population; N2 = Number of patients in the CE-EOT population; N3 = Number of patients in the CE-SFU population; SFU = Short Term Follow-up.

All primary endpoints were met and secondary analyses were concordant, indicating that these data are robust. Taken together, these studies provide convincing evidence of the efficacy of dalbavancin in the treatment of ABSSSI.

6.7.2 Clinical Efficacy Outcomes by Baseline Pathogen across Studies

Clinical efficacy rates by baseline pathogen for the ABSSSI and cSSSI studies were high and similar to that of the comparator agents (Table 40). Combined by-pathogen investigator-assessed success rates for ABSSSI patients receiving dalbavancin with *S. aureus* at Baseline were 97.9% for the 2 ABSSSI studies combined versus 96.6% for comparator. Rates of eradication for patients with MRSA for dalbavancin and comparator were 97.3% and 98.0% respectively. *S. pyogenes* eradication rates, an organism much more difficult to culture from patients with cellulitis or erysipelas, but likely contributing to a majority of these disease presentations, were 100% (19/19) and 92.3% (12/13) in the two groups, respectively.

Table 40. Investigator Assessment of Clinical Outcomes at End of Treatment by Key Target Pathogen in Patients with Monomicrobial ABSSSI[a], Studies DUR001-301/DUR001-302 (pooled)

Baseline pathogen	Patients, n (%)	
	DUR001-301 and DUR001-302 (pooled)	
	Dalbavancin	Vancomycin/Linezolid
S. aureus (All)	187/191 (97.9)	171/177 (96.6)
MRSA	72/74 (97.3)	49/50 (98.0)
MSSA	115/117 (98.3)	121/126 (96.0)
S. pyogenes	19/19 (100)	12/13 (92.3)
S. agalactiae	6/7 (85.7)	1/2 (50.0)
S. dysgalactiae	1/1 (100)	1/1 (100)
S. anginosus group	9/9 (100)	9/9 (100)
S. anginosus	2/2 (100)	2/2 (100)
S. constellatus	5/5(100)	6/6 (100)
S. intermedius	2/2 (100)	1/1 (100)

6.7.2.1 Patients with Bacteremia at Baseline

Bacteremic status was assessed in the Micro-ITT population in six phase 2/3 studies.

Except for Study VER001-4 (CRBSI), bacteremia rates of 1% to 5% in these studies are consistent with historical rates of bacteremia in this indication (Table 41).

- In Study DUR001-301 (ITT population), 8 (2.8%) patients in the dalbavancin group and 6 (2.1%) patients in the active comparator group were bacteremic.
- In Study DUR001-302 (ITT population), 21 (5.7%) patients in the dalbavancin group and 13 patients (3.5%) patients in the active comparator group were bacteremic.

- In Study VER001-9 (ITT population), 12 (2.1%) patients in the dalbavancin group and 6 (2.1%) patients in the linezolid group were bacteremic with a Gram-positive pathogen at Baseline. In 11/18 (61.1%) of these cases, the pathogen isolated was *S. aureus* and, of these, 6 (54.5%) were MRSA. Other pathogens included *S. agalactiae* (n=3), *S. pyogenes* (n=2), *Streptococcus* group G (n=1) and *Streptococcus* group C (n=1).
- In Study VER001-16, 1 patient in the dalbavancin group was bacteremic with a Gram-positive pathogen (MRSA) at Baseline.
- In Study VER001-8 (ITT population), 3 (0.8%) patients in the dalbavancin group and 1 (0.5%) patient in the cefazolin group were bacteremic with a Gram-positive pathogen at Baseline. MRSA was isolated from a Baseline blood culture for 2/4 patients (50.0%), *S. pyogenes* for 1/4 patients (25.0%) and Viridans *Streptococcus* for 1/4 patients (25.0%).
- Data on bacteremic status were not collected in Study VER001-5.

In Study VER001-4 (CRSBI), 23/33 (69.7%) patients in the dalbavancin group and 28/34 (82.4%) patients in the vancomycin group were bacteremic with a Gram-positive pathogen at Baseline.

Table 41 Summary of Patients With Bacteremia in SSSI Program

MicroITT		EOT		
	Total Number of Subjects with Baseline Bacteremia	Number with Follow-up Blood Cultures	Number (%) with Documented Clearance of Bacteremia	Number (%) with Documented Persistence of Bacteremia
DUR001-301				
Dalbavancin	8	5	5/5 (100)	0
Vancomycin/Linezolid	6	4	3/4 (75)	1/4 (25)
DUR001-302				
Dalbavancin	21	17	17/17 (100)	0
Vancomycin/Linezolid	13	10	9/10 (90.0)	1/10 (10)
Study VER001-9				
Dalbavancin	12	12	12/12 (100)	0
Linezolid	6	6	6/6 (100)	0
Study VER001-16				
Vancomycin	1	1	1/1 (100)	0
	0	0	0	0
Study VER001-8				
Dalbavancin	3	2	2/2 (100)	0
Cefazolin	1	1	0/1 (0.0)	1/1 (100)
Total				
Dalbavancin	45	37	37/37 (100)	0
Comparator	26	21	18/21 (85.7)	3/21 (14.3)

Source: Dunne and Puttagunta, IDSA Poster 2013.
Abbreviations: EOT = end of treatment; SSSI = skin and skin structure infections

Across the clinical program in skin infections, all of the patients in the dalbavancin group with baseline gram-positive bacteremia who had follow-up blood cultures available for evaluation had documented clearance of bacteremia, while 3 of 21 such patients in the comparator group had documented persistence.

Table 42 describes the clinical outcomes specifically for patients with *S. aureus* bacteremia at baseline in the clinical development program (ABSSSI studies DUR001-301/302 and VER001-9 and CRBSI study VER001-4). Of the 24 patients treated with dalbavancin with *S. aureus* bacteremia at baseline who had follow up blood cultures, all 24 patients (100%) were documented to have cleared their bacteremia, compared with 19 of 20 patients with *S. aureus* bacteremia who were treated with comparators. For dalbavancin-treated patients, 19/22 patients (86.4%) were clinical successes at EOT, versus 18/23 patients treated with comparators (78.3%). Though based on only 22 and 23 patients, the clinical success rates were similar to the overall success rate for patients in the program.

Table 42. Documented Clearance and Clinical Outcome of *S. aureus* Bacteremia in Patients With Follow-up Blood Cultures

	Dalbavancin		Comparator	
Infection	Clearance of Bacteremia[a]	Clinical Success at EOT[b]	Clearance of Bacteremia[a]	Clinical Success at EOT[b]
ABSSSI				
DUR001-301	3/3	2/3	2/3	3/3
DUR001-302	7/7	5/6	6/6	5/6
cSSSI (VER001-9)	4/4	3/4	2/2	2/2
CRBSI (VER001-4)	10/10	9/9	9/9	8/12
Total	24/24 (100%)	19/22 (86.4%)	19/20 (95%)	18/23 (78.3%)

[a] Patients with follow-up blood culture (post-baseline).
[b] Clinically evaluable population (those with missing data excluded from analysis) of patients with a positive blood culture at baseline

Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; cSSSI = complicated bacterial skin and skin structure infections; CRBSI = Catheter-related bloodstream infection

From Table 42 above, 3 dalbavancin-treated patients with *S.aureus* bacteremia were clinical failures at EOT. None of these failures were a result of persistent bacteremia, but rather due to disease under study or other ancillary reasons as described below.

- The one subject from Study DUR001-301 in the dalbavancin group with an outcome of clinical failure at EOT was a 19-year-old man with history of spina bifida and a chronic right sacral decubitus ulcer who was taken off study drug therapy on Day 4 when blood cultures drawn at Baseline were found to be growing MSSA. All blood cultures drawn subsequently remained sterile, but an infectious disease consultant recommended taking the patient off blinded study drug therapy and started him on cefazolin. The patient was considered an early responder at the 48 to 72 hour time point, as lesion size improved and fever resolved. However, the patient was considered a clinical failure on Day 6 due to receiving a new nonstudy systemic antibacterial treatment for the ABSSSI between the

first dose and the EOT, had unresolved local signs of fluctuance and localized heat/warmth at EOT, had local signs of tenderness to palpitation and swelling/induration that were worse than mild at EOT, and had surgical intervention on Day 6.

- The one subject from Study DUR001-302 in the dalbavancin group with an outcome of clinical failure at EOT was a 31 year old woman with history of diabetes mellitus enrolled with a major abscess. One of 4 Baseline blood cultures grew MSSA and 4 sets of blood cultures on Day 4 were sterile. Lesion size decreased to 0 and all local signs of ABSSSI improved on Day 14, but patient was a failure because erythromycin was prescribed from Day 13 through Day 21 for primary ABSSSI for unclear reasons.

- The one subject from Study VER001-9 in the dalbavancin group with an outcome of clinical failure at EOT was a 43 year old woman with a major abscess on her back with baseline blood cultures revealing MRSA. Subsequent blood cultures drawn on Day 4 were sterile but patient was declared a clinical failure due to "worsening abscess" on Day 5 and switched to trimethoprim/sulfamethoxazole and vancomycin.

6.7.3 Persistence of Efficacy

Persistence of efficacy was examined in the phase 3 studies DUR001-301, and DUR001-302 by evaluating patients at a late follow-up assessment (LFU). For those patients considered by the investigator to have demonstrated a successful clinical response at TOC (and who were not a failure at EOT), a LFU visit was performed at Day 70 (window Day 60-Day 88) in Studies DUR001-301 and DUR001-302.

In ABSSSI Studies DUR001-301 and DUR001-302, in both the CE and ITT populations, >90% of eligible dalbavancin treated patients were assessed at LFU. In the CE populations in these 2 studies, the percentage of LFU failures, ie, patients who reported antibiotic use for ABSSSI between SFU and LFU, was < 1.0% in each treatment group.

6.7.4 Emergence of Resistance

There was no emergence of resistance (defined as a ≥ 4-fold increase in MIC in the identical pathogen from Baseline to any subsequent study time point) in either the 2 pivotal ABSSSI studies or the other 4 SSSI studies (VER001-9, VER001-16, VER001-8 and VER001-5).

6.7.5 Primary Efficacy Analysis across Studies by Subgroups

The analyses of covariates also demonstrated efficacy in relevant subpopulations. There were no significant associations between clinical response rates and diabetes, gender, or race/ethnicity. While response rates were lower in patients ≥ 65 years, no differences between treatment groups within a study were evident.

In the ABSSSI studies (DUR001-301 and DUR001-302), response rates at 48 to 72 hours and at the EOT visit were generally similar for patients enrolled in US/Canada relative to rest-of-world (ROW). The differences in clinical response outcomes by geographical location may have been influenced by a number of different factors, including antibiotic-prescribing practices (eg, duration of treatment), patient-demand, and health-belief

differences, between North America and the participating European countries. Because dalbavancin is not hepatically metabolized, the variation in phenotypic expression of CYP450 isoenzymes would not be anticipated to impact dalbavancin levels and therefore should not impact efficacy.

6.7.6 Secondary Efficacy Analyses by Subgroups

As noted above, clinical response in the ITT population at 48 to 72 hours and clinical success in the CE population at EOT and SFU for the integrated phase 3 (DUR001-301/302) analysis set was not affected by age, gender, race, ethnicity, or geographic region and were similar between treatment groups for each demographic parameter (Table 43). Clinical success at SFU was generally higher than at EOT for each parameter.

Table 43 Clinical Response at 48 to 72 Hours and Clinical Status of Success at the End-of-Treatment Visit and the Short-Term Follow-up Visit by Patient Demographics in Phase 3 ABSSSI Studies DUR001-301 and DUR001-302

	Clinical Response at 48 to 72 Hours (ITT Population)		Clinical Success at EOT (CE-EOT Population)		Clinical Success at SFU (CE-SFU Population)	
	Dalbavancin n/N (%)	Vancomycin/ Linezolid n/N (%)	Dalbavancin n/N (%)	Vancomycin/ Linezolid n/N (%)	Dalbavancin n/N (%)	Vancomycin/ Linezolid n/N (%)
Overall	525/659 (79.7)	521/653 (79.8)	517/570 (90.7)	502/545 (92.1)	495/520 (95.2)	477/501 (95.2)
Age distribution:						
<65 years	436/552 (79.0)	422/529 (79.8)	427/473 (90.3)	406/440 (92.3)	411/434 (94.7)	386/404 (95.5)
≥65 years	89/107 (83.2)	99/124 (79.8)	90/97 (92.8)	96/105 (91.4)	84/86 (97.7)	91/97 (93.8)
Gender:						
Male	314/393 (79.9)	305/374 (81.6)	304/338 (89.9)	282/308 (91.6)	293/306 (95.8)	275/283 (97.2)
Female	211/266 (79.3)	216/279 (77.4)	213/232 (91.8)	220/237 (92.8)	202/214 (94.4)	202/218 (92.7)
Race:						
White	477/592 (80.6)	467/579 (80.7)	471/516 (91.3)	453/488 (92.8)	445/467 (95.3)	431/449 (96.0)
Black or African American	20/29 (69.0)	28/36 (77.8)	21/23 (91.3)	25/27 (92.6)	21/23 (91.3)	23/24 (95.8)
American Indian or Alaska Native	19/28 (67.9)	23/32 (71.9)	19/25 (76.0)	21/27 (77.8)	22/23 (95.7)	21/25 (84.0)
Asian	5/5 (100.0)	1/4 (25.0)	3/3 (100.0)	1/1 (100.0)	3/3 (100.0)	0/1 (0.0)
Native Hawaiian or Other Pacific Islander	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Other	3/4 (75.0)	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)	3/3 (100.0)	1/1 (100.0)
Ethnicity:						
Hispanic or Latino	105/122 (86.1)	87/106 (82.1)	95/101 (94.1)	78/86 (90.7)	86/90 (95.6)	72/75 (96.0)
Not Hispanic or Latino	420/537 (78.2)	434/547 (79.3)	422/469 (90.0)	424/459 (92.4)	409/430 (95.1)	405/426 (95.1)
Geographic Region:						
US/Canada	196/238 (82.4)	189/235 (80.4)	175/193 (90.7)	169/185 (91.4)	161/170 (94.7)	158/165 (95.8)
Rest of World	329/421 (78.1)	332/418 (79.4)	342/377 (90.7)	333/360 (92.5)	334/350 (95.4)	319/336 (94.9)

6.7.7 Clinical Efficacy across Studies by Infection Subtype and Analysis Population

Clinical response in the ITT population at 48 to 72 hours and clinical success in the CE population at EOT and SFU for the integrated phase 3 DUR001-301/302 analysis set were generally higher for patients with major abscess or no SIRS at Baseline, but was not affected by outpatient status (Table 44). Clinical response in the ITT population at 48-72 hours and clinical success in the CE population at EOT and SFU were similar between treatment groups for each parameter. Clinical success at SFU was generally higher at SFU than at EOT for each parameter.

Where applicable, secondary efficacy variables were analyzed using the same methodology as for the primary endpoint. However, it should be noted that the studies were not intended to demonstrate non-inferiority for secondary efficacy variables.

Table 44 Clinical Response at 48 to 72 Hours and Clinical Success at the End-of-Treatment Visit and the Short-Term Follow-up Visit by Infection Subtype and Analysis Population in Phase 3 ABSSSI Studies DUR001-301 and DUR001-302 (pooled)

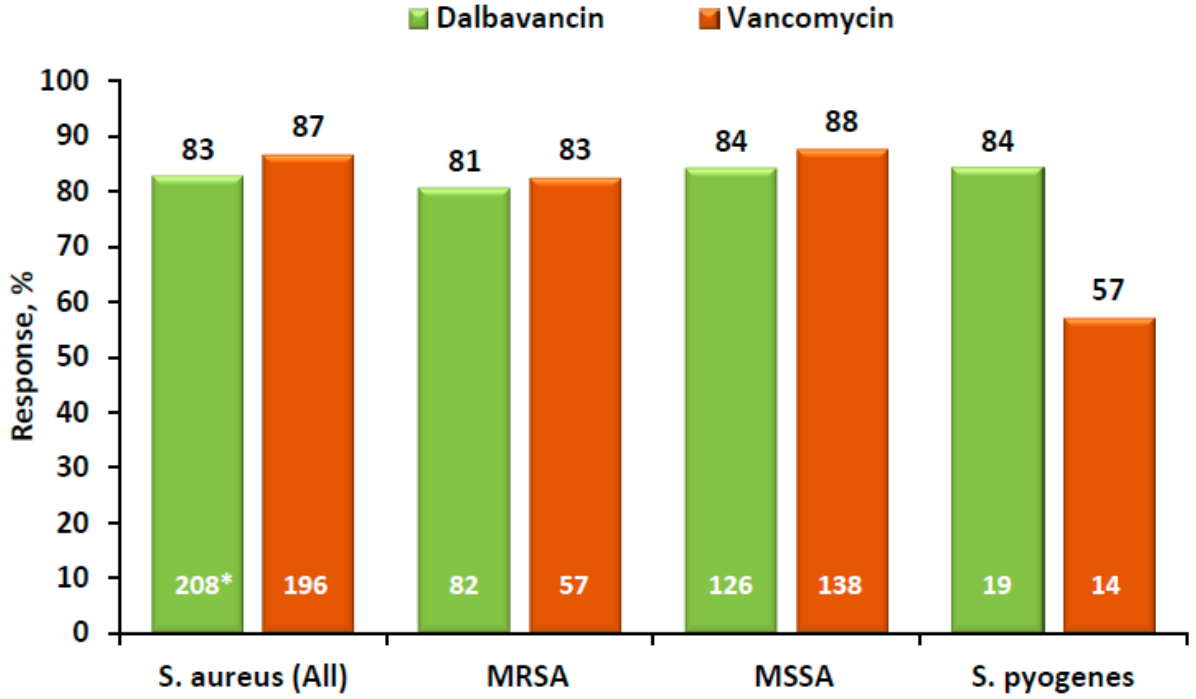
	Clinical Response at 48 to 72 Hours (ITT Population)		Clinical Success at EOT (CE-EOT Population)		Clinical Success at SFU (CE-SFU Population)	
	Dalbavancin n/N (%)	Vancomycin/ Linezolid n/N (%)	Dalbavancin n/N (%)	Vancomycin/ Linezolid n/N (%)	Dalbavancin n/N (%)	Vancomycin/ Linezolid n/N (%)
Overall	525/659 (79.7)	521/653 (79.8)	517/570 (90.7)	502/545 (92.1)	495/520 (95.2)	477/501 (95.2)
Infection Type :						
Cellulitis	281/354 (79.4)	269/349 (77.1)	294/324 (90.7)	276/301 (91.7)	273/291 (93.8)	261/277 (94.2)
Treatment Difference (95% CI)	2.2 (-3.9, 8.3)		-1.0 (-5.5, 3.6)		-0.4 (-4.5, 3.7)	
Major Abscess	133/163 (81.6)	149/173 (86.1)	125/133 (94.0)	133/139 (95.7)	117/121 (96.7)	125/128 (97.7)
Treatment Difference (95% CI)	-4.7 (-12.7, 3.3)		-1.9 (-8.0, 3.7)		-1.4 (-6.8, 3.4)	
Wound Infection	111/142 (78.2)	103/131 (78.6)	98/113 (86.7)	93/105 (88.6)	105/108 (97.2)	91/96 (94.8)
Treatment Difference (95% CI)	-0.7 (-10.4, 9.3)		-1.6 (-10.6, 7.3)		2.4 (-3.4, 9.2)	
SIRS at Baseline:						
Yes	248/332 (74.7)	264/336 (78.6)	257/296 (86.8)	263/290 (90.7)	257/271 (94.8)	258/273 (94.5)
No	277/327 (84.7)	257/317 (81.1)	260/274 (94.9)	239/255 (93.7)	238/249 (95.6)	219/228 (96.1)
Outpatient status:						
All Doses as Outpatients	131/160 (81.9)	123/157 (78.3)	125/138 (90.6)	114/126 (90.5)	115/121 (95.0)	107/111 (96.4)
Inpatient for Any Dose	394/499 (79.0)	398/496 (80.2)	392/432 (90.7)	388/419 (92.6)	380/399 (95.2)	370/390 (94.9)

6.7.8 Clinical Efficacy across Studies by Baseline Pathogen

In all phase 3 studies, *S. aureus* was the most common Gram-positive pathogen, isolated from 75.5% of patients with a pathogen at Baseline (833/1104 patients). The prevalence of MRSA was influenced in part by the study design, ranging from 278/492 of isolates (56.5%) in VER001-9, 83/250 (33.2%) of patients in DUR001-301, and 74/263 (28.1%) of patients in DUR001-302.

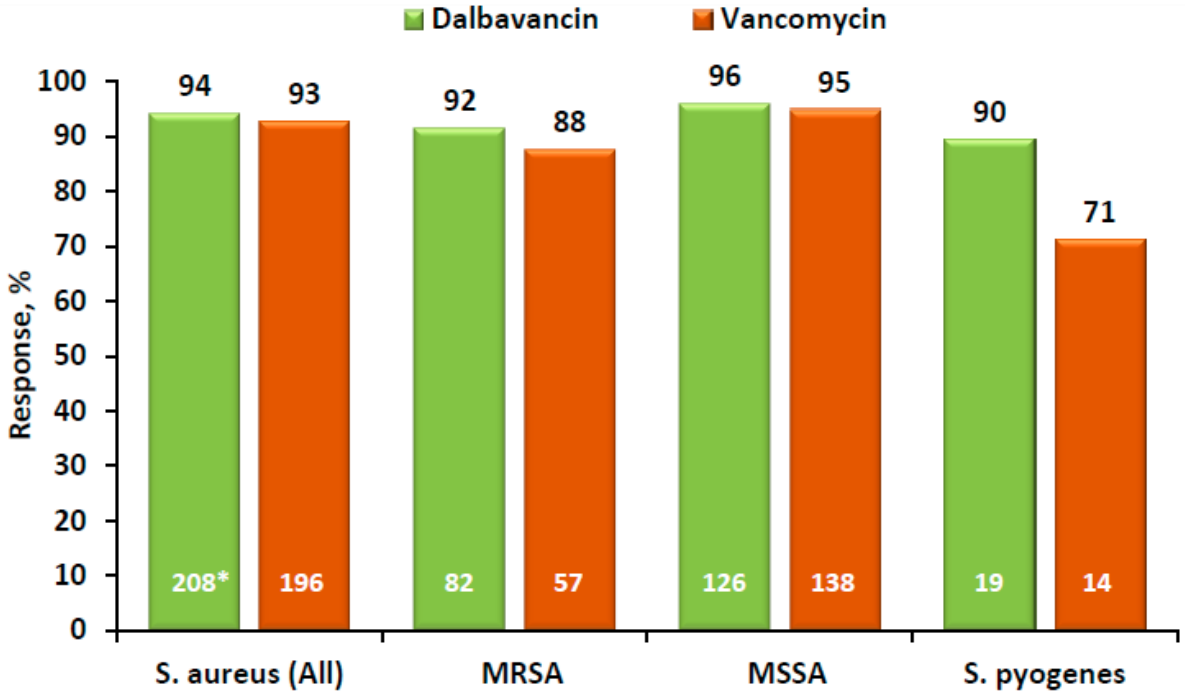
When assessed by pathogen isolated at baseline, the proportion of patients in the ABSSSI trials treated with dalbavancin who achieved the primary endpoint at 48-72 hours was similar to those treated with vancomycin/linezolid including 83% of the 208 patients with *S. aureus* and 81% of the 82 patients with MRSA (Figure 23).

Figure 23. Clinical Success at the Primary Endpoint at 48-72 Hours, by Pathogen, Studies DUR001-301/302 (pooled)



Similarly, the proportion of patients treated with dalbavancin who achieved a ≥ 20% reduction in lesion size at 48-72 hours was similar to those treated with vancomycin/linezolid including 94% of the 208 patients with *S. aureus* and 92% of the 82 patients with MRSA (Figure 24).

Figure 24. Proportion of Patients Achieving ≥ 20% Reduction in Lesion Size at 48-72 Hours by Pathogen, Studies DUR001-301/302 (pooled)



6.7.8.1 Clinical Response at End of Treatment by Baseline Pathogen and Geographic Location

In the ABSSSI trials, the prevalence of MRSA varied markedly by geographical location. However, despite this variation of MRSA distribution (high in North America and lower in Europe and Asia), clinical responses were consistent between patients with MRSA and patients with MSSA treated with either dalbavancin or vancomycin/linezolid, supporting the generalizability of these results in the 2 identically-designed trials (Table 45). Eradication and presumed eradication rates for MRSA, as reflected by the clinical response rates, were high.

Table 45. Clinical Status at EOT by Key Target Pathogens in the ME Population by Geographic Location: Integrated Study DUR001-301 and Study DUR001-302 (pooled)

Region: North America Gram-positive organisms (aerobes)	DUR001-301 and DUR001-302 (pooled)			
	Dalbavancin N = 133		Vancomycin/Linezolid N = 128	
Baseline Pathogen	N1	n (%)	N1	n (%)
Staphylococcus aureus	116	106 (91.4)	109	102 (93.6)
MRSA	75	69 (92.0)	53	52 (98.1)
MSSA	41	37 (90.2)	55	49 (89.1)
Streptococcus agalactiae	2	2 (100.0)	3	2 (66.7)
Streptococcus anginosus group	12	11 (91.7)	17	16 (94.1)
Streptococcus anginosus	3	3 (100.0)	3	3 (100.0)
Streptococcus constellatus	8	7 (87.5)	13	12 (92.3)
Streptococcus intermedius	4	3 (75.0)	3	3 (100.0)
Streptococcus pyogenes	0	0 (0.0)	2	2 (100.0)
Region: Europe Gram-positive organisms (aerobes)	**Dalbavancin N = 143**		**Vancomycin/Linezolid N = 126**	
Baseline Pathogen	N1	n (%)	N1	n (%)
S. aureus	105	93 (88.6)	105	97 (92.4)
MRSA	3	3 (100.0)	1	1 (100.0)
MSSA	102	90 (88.2)	104	96 (92.3)
S. agalactiae	9	6 (66.7)	3	3 (100.0)
S. anginosus group	4	4 (100.0)	3	3 (100.0)
S. anginosus	2	2 (100.0)	0	0 (0.0)
S. constellatus	2	2 (100.0)	1	1 (100.0)
S. intermedius	0	0 (0.0)	2	2 (100.0)
Streptococcus dysgalactiae	3	3 (100.0)	0	0 (0.0)
Strepotococcus pyogenes	34	33 (97.1)	30	27 (90.0)

Table 45. Clinical Status at EOT by Key Target Pathogens in the ME Population by Geographic Location: Integrated Study DUR001-301 and Study DUR001-302 (pooled)

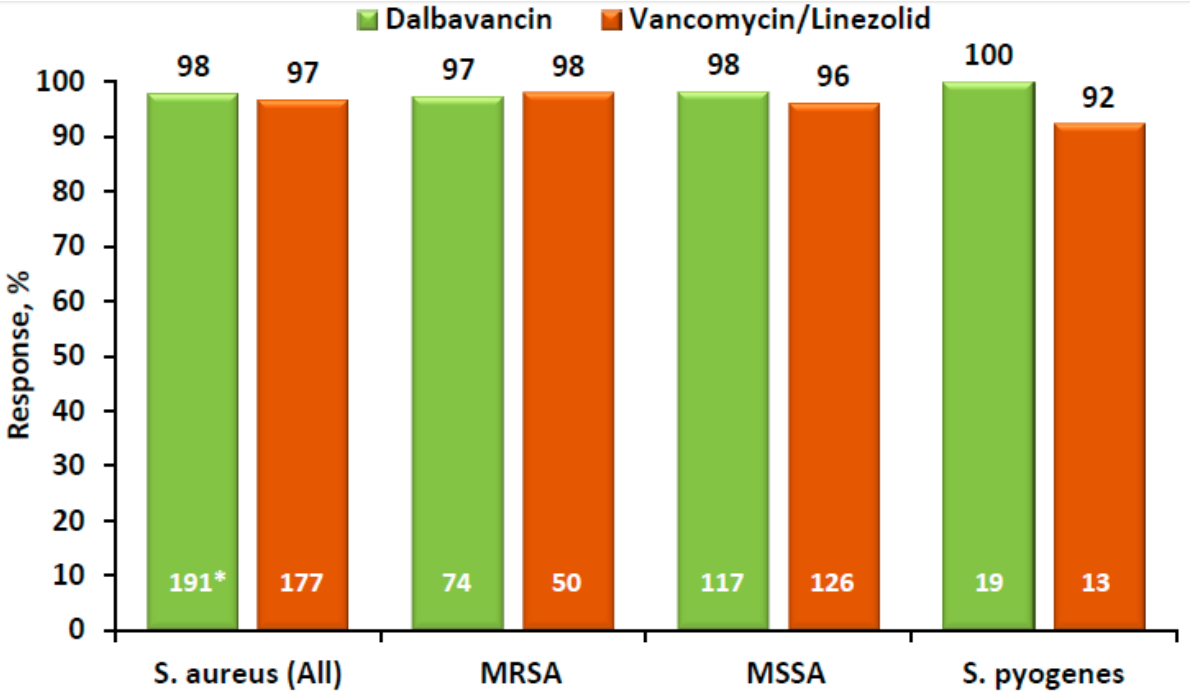
Region: Other Gram-positive organisms (aerobes)	Dalbavancin N = 3		Vancomycin/Linezolid N = 5	
Baseline Pathogen	N1	n (%)	N1	n (%)
S. aureus	1	1 (100.0)	2	1 (50.0)
MRSA	0	0 (0.0)	1	1 (100.0)
MSSA	1	1 (100.0)	1	0 (0.0)
S. agalactiae	1	1 (100.0)	1	1 (100.0)
S. anginosus group	1	1 (100.0)	0	0 (0.0)
S. anginosus	1	1 (100.0)	0	0 (0.0)
S. constellatus	1	1 (100.0)	0	0 (0.0)
S. dysgalactiae	0	0 (0.0)	1	1 (100.0)

Notes: Percentages are calculated as 100 x (n/N1).
Abbreviations: ME = microbiologically evaluable; N = Number of patients in the microbiologically evaluable population; N1 = Number of patients with the specific pathogen; n = Number of clinical status of success for the specific pathogen

6.7.8.2 Investigator Assessment of Clinical Success at End of Treatment by Baseline Pathogen

Investigator assessment of clinical success by baseline pathogen at EOT was similar between treatment groups across the 2 ABSSSI trials. In the pooled results from ABSSSI Studies DUR001-301 and DUR001-302, investigator assessment of clinical success at EOT for *S. aureus* was 97.9% and 96.6% for dalbavancin- and comparator-treated patients, respectively. For patients with an infection attributed to MRSA, investigator assessment of success at EOT was 97.3% and 98.0% for dalbavancin- and comparator-treated patients, respectively. The same results were observed in an analysis of the pooled outcomes from DUR001-301/302 (Figure 25).

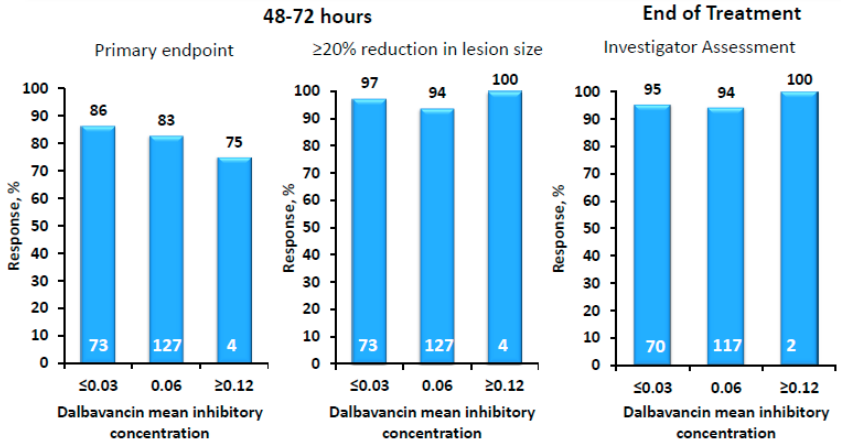
Figure 25. Clinical Success by Baseline Pathogen: Investigator Assessment at End of Treatment (ME) ABSSSI, DUR001-301/302 (pooled)



6.7.8.3 Clinical Response at 48-72 hours by Dalbavancin MIC: *S. aureus*

For patients with *S. aureus* isolated at baseline, clinical response at 48-72 hours was analyzed by pathogen MIC (Figure 26). For the vast majority of organisms, susceptibility test results were almost evenly divided between 0.03 and 0.06 µg/mL, with only a few with susceptibilities at either 0.12 or 0.25 µg/mL. The MIC data assessed by the primary endpoint or by a ≥ 20% reduction in lesion size were similar.

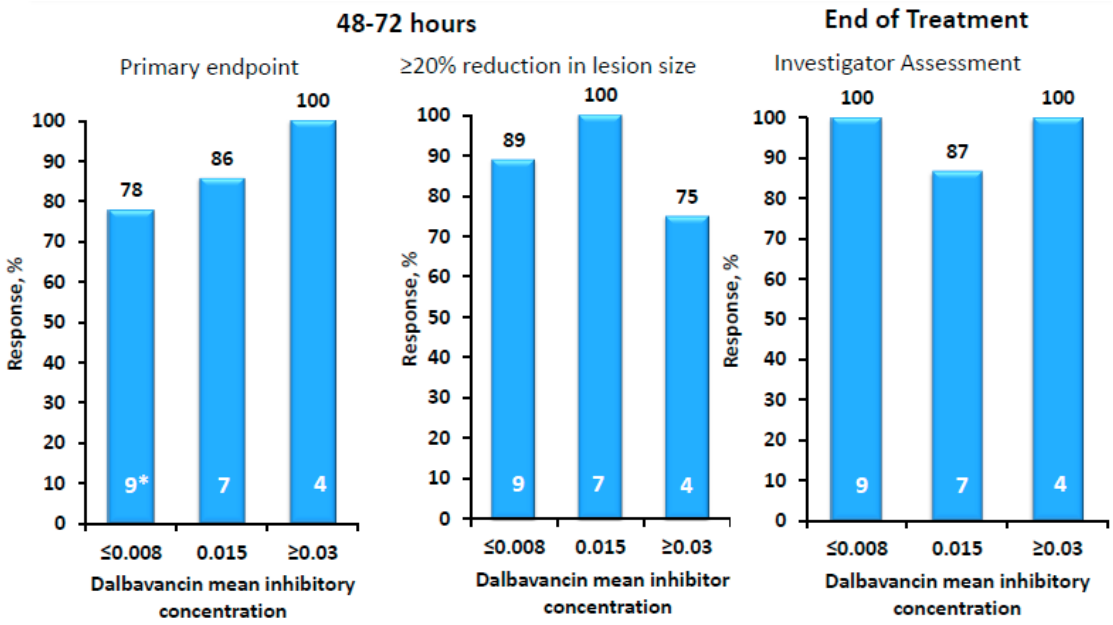
Figure 26. Clinical Response at 48-72 hours by Dalbavancin MIC: *S. aureus* Studies DUR001-301/302 (pooled)



No organism isolated at Baseline was subsequently recovered at a later timepoint with an MIC of greater than 2-fold that of the initial isolate, consistent with the expectations set by the in vitro passage experiments (Section 1.5.5), which implied that reduction in susceptibility over time would be unlikely.

For *S. pyogenes*, there were fewer pathogens overall, thereby affording very small subgroups by MIC. Nevertheless, the results suggest similar outcome rates by MIC (Figure 27).

Figure 27. Clinical Response at 48-72 Hours by Dalbavancin MIC: *S. pyogenes*: Studies DUR001-301/302 (pooled)



6.8 Efficacy Conclusions

All studies were well-designed and well-conducted. Trial designs were reflective of regulatory agency guidance that existed at the time each study was conducted. The analysis plans were prospectively described and the results presented include similarities and differences across relevant subgroups. Dalbavancin was effective for the treatment of patients with ABSSSI or cSSSI and found to be statistically non-inferior to comparator treatments. The patient populations represented a broad cross-section of serious SSSIs, including major abscesses, cellulitis and traumatic wound infections. Response rates were high and consistent across treatment groups for the subgroups. Durability of clinical response was demonstrated in both treatment groups.

In Studies DUR001-301 and 302, an early clinical outcome (clinical success, including cessation of the spread of the lesion and absence of fever) at 48-72 hours in ITT population was selected as the primary endpoint, in accordance with the August 2010 Draft Guidance, and FDA SPA agreements. In addition, secondary analyses prospectively performed for both studies on the new primary endpoint (≥ 20% reduction in lesion area from Baseline at 48-72

hours in patients who were alive and did not receive rescue therapy) from the October 2013 Final Guidance also demonstrated non-inferiority to the comparator treatment.

Over 85% of patients within each treatment group completed each study and the percentages of patients either discontinuing from the study, or withdrawing from study medication, were well-balanced across treatment groups within a study. In addition, the percentages of patients included in the MicroITT population and the CE and ME populations were usually well-balanced across treatment groups within a study.

Extrapolation from human blister fluid shows dalbavancin levels to be approximately 60% of plasma levels (Section 5.2). In one in vivo model in which the dose given was not adequate to sterilize, regrowth began when levels were ~3 µg/mL, suggesting that the therapeutic target is a level greater than this. Whether one estimates free drug in tissues, or examines drug levels in an in vivo model, the timing of the TOC assessment is supported.

All of the phase 3 studies enrolled substantial numbers of patients with comorbidities, indicating similarities in the patient populations, and demonstration of efficacy in important target patient populations.

In Study VER001-9, particular attention was given to selection of the appropriate timing of the TOC assessment, which was scheduled for 14 ± 2 days after completion of therapy. Timing of this assessment was based upon FDA Guidance documents on uSSSI and cSSSI (US FDA, 1998) which recommended that the TOC visit should occur 14–21 days after completion of therapy for drugs with a long $t_{1/2}$. The timing was also based upon a need to allow adequate time for resolution of signs and symptoms of the SSSI under study while ensuring patient compliance with this visit, and minimizing those patients who might be lost to follow-up with a later TOC assessment. In order to document durability of response, the LFU assessment was added; it is notable that the failure or 'relapse rate' was extremely low (<1%) for both dalbavancin and comparator in the 3 phase 3 studies.

7 CLINICAL MICROBIOLOGY

An overview of this Clinical Microbiology section is presented in Section 1.7.2.

7.1 Susceptibility Determination Methodology

The principal target pathogens in ABSSSI are staphylococci and streptococci. Broth microdilution, with CLSI methodology (CLSI 2012a, CLSI 2013), was used as the standard for determining activity of antibacterial agents against bacteria that grow aerobically.

Analytical studies demonstrated that the solubility limit of dalbavancin at neutral pH (such as in broth media) was approximately 20 µg/mL. Therefore, using the standard dilution scale, the maximum concentration of dalbavancin that should be tested is 16 µg/mL. In order to ensure solubility of all dilutions, DMSO is used as the intermediate diluent for dalbavancin (CLSI 2012a, CLSI 2013).

During the course of development of dalbavancin, it was observed that a small amount of a wetting agent, such as polysorbate-80 (P-80), when included in the inoculum and diluent, ensured more reproducible dalbavancin MICs for quality control (QC) strains and other isolates when using the frozen panels. Use of P-80 in the inoculum water has been standard practice in many laboratories since the microdilution method for MIC determination was first validated (Barry 1978), and does not appear to affect the potency of most other antimicrobial agents. The methodology for dalbavancin has now been standardized to include 0.002% polysorbate-80 (P-80) in the dalbavancin dilution series rather than introducing it in the inoculum.

7.2 Surveillance Studies

7.2.1 Worldwide Surveillance Studies

Prospective worldwide surveillance of the in vitro potency of dalbavancin, in comparison with other antimicrobial agents, was begun in 2002 and has continued through 2012 as of the preparation of this Application. Table 46 lists the various studies in which the in vitro potency (MIC) of dalbavancin was determined, along with the number of isolates included. All data presented reflect state of the art methodology at the time they were generated. The most consistent MIC data, across studies, was obtained using broth microdilution methodology with addition of P-80 or with validated dry-form microtiter panels. However, in virtually all studies, regardless of method, dalbavancin had in vitro potency greater than most comparators against the principal target organisms (staphylococci and streptococci). The different test conditions that were used are indicated in Table 46 and in text descriptions of individual studies.

Table 46 Summary of Studies of Dalbavancin Potency (MIC) in Vitro

Study	Source of Isolates	Number of Isolates	Methodology	References
Worldwide surveillance (2002-2012)	Blood, respiratory, skin, urine, other	>150,000	Broth microdilution (dry-form panels)	R. Jones, JMI Laboratories
European Surveillance (2011-2012)	Blood, respiratory, skin/wound, other	1,166	Broth microdilution with P-80	Data on file
CANWARD Canadian surveillance studies (2005-2009)	Blood, respiratory, skin, urine	>9,000	Broth microdilution with P-80	Zhanel 2008; Weshnowesky 2010; Karlowsky 2011
Belgian *S. aureus* surveillance (2008)	Blood, skin, nares, urine, other	525	Broth microdilution (P-80 not indicated)	Data on file
Korean MRSA study	Blood	569	Broth microdilution (no P-80)	Chong 2012
Vicuron in-house study, including Eurostudy enterococcus surveillance	Various; enterococci from feces	401	Broth microdilution (no P-80); agar (anaerobes)	Data on file
Primary pathogens, resistant organisms (NARSA collection)	Blood, CSF, SSSI, peritoneal fluid, respiratory, urine, bone/joint, other	1,093	Broth microdilution (dry-form panels)	Data on file
European retrospective surveillance, GR Micro	Blood, skin, other	1266	Broth microdilution (dry-form panels)	Data on file
UK retrospective surveillance streptococci/staphylococci	Clinical specimens	277	Agar dilution	Mushtaq, 2004
Staphylococci, Hershey PA	Blood, skin, respiratory, urine, bone, other	146	Broth microdilution (dry-form panels)	Lin 2005a
CA-MRSA	Various	23	Broth microdilution (dry-form panels)	Saravolatz 2005
Staphylococci	Istanbul	453	Broth microdilution (P-80 in medium only; dilutions in water)	Aktas 2010
CA-MRSA, MDR HA-MRSA	Detroit Medical Center	220	Broth microdilution (P-80 in medium only)	Huang 2010
Viridans group streptococci, Sweden	Blood	129	Agar dilution	Westling 2006

Table 46 Summary of Studies of Dalbavancin Potency (MIC) in Vitro

Study	Source of Isolates	Number of Isolates	Methodology	References
S. epidermidis, Sweden	Prosthetic joint infection	33	E-test	Hellmark 2009
S. pneumoniae, Hershey PA	Various	307	Broth microdilution (dry-form panels)	Lin 2005b
Gram-positive cocci	Various	161	Broth microdilution (no P-80)	Candiani 1999
University of Iowa isolates	Various	1061	Broth microdilution	Jones 2001
Vicuron in-house study	Blood, other	45	Broth microdilution (no P-80)	Data on file
Vicuron in-house study	Various	216	Broth microdilution (no P-80)	Data on file
Bacillus. anthracis	Various	27	Broth microdilution	Heine 2010
Anaerobic, aerobic secondary pathogens	Various	245	Agar dilution (anaerobes); Broth microdilution (dry-form panels)	Data on file
Anaerobes, corynebacteria	Clinical specimens	290	Agar dilution	Goldstein 2003
Diabetic foot isolates	Diabetic foot	329	Agar dilution (anaerobes); Broth microdilution (dry-form panels)	Goldstein 2006
Anaerobe methodology	Various	15	Broth and agar dilution	Data on file
M. catarrhalis	Respiratory	10	Broth microdilution with P-80	Koeth, LSI ECCMID abstract, 2012a
N. gonorrhoeae	Various	31	Agar, broth microdilution with P-80	Koeth – IDSA abstract, 2013
Resistant organisms from 2001-2002 SENTRY	Blood, respiratory, skin, urine, other	380	Broth microdilution (dry-form panels)	Jones 2003, Streit 2005
Resistant *S. aureus*	Various	42	Broth microdilution (frozen panels)	Data on file
hVISA	Various	36	Broth microdilution (P-80 not specified)	Campanile, 2010

7.2.1.1 Worldwide Surveillance Studies of Dalbavancin Activity Against Gram-Positive Aerobic Bacteria

The most extensive surveillance study of dalbavancin activity is the SENTRY study, which has been continuing, prospectively, since 2002. Other prospective surveillance studies have been conducted in Europe, Canada and a few other countries. Additionally, there have been retrospective studies in which large culture collections were sampled, sometimes with the inclusion of challenge isolates.

For the purpose of this briefing document, results for the major Gram-positive SSSI pathogens, streptococci and staphylococci from the larger surveillance studies from the United States and Europe are summarized below (Section 7.2.2).

7.2.2 SENTRY Study

The potency of dalbavancin and selected comparators against Gram-positive aerobic bacteria has been evaluated in an ongoing prospective worldwide surveillance study initiated in 2002 (the SENTRY study, conducted by JMI Laboratories, North Liberty, Iowa USA). This program collects isolates from several hundred hospitals. Most of the data available, through 2012, are for isolates from the United States and Europe. All of the strains tested were unique patient isolates; the sources were mainly bloodstream, respiratory and SSSI infections. Isolates were tested by the broth microdilution method (CLSI 2012a, CLSI 2013) using validated dry-form microtiter panels (Jones 2004).

Susceptibility data is available for more than 126,000 isolates of Gram-positive aerobic cocci, including more than 60,000 *S. aureus* and more than 7,000 β-hemolytic streptococci. Over 70,000 of the isolates were collected between 2007 and 2012. In this and several other studies to be described, the activity of dalbavancin was compared to that of a number of other antibacterial agents that are utilized to treat Gram-positive infections, including the glycopeptides vancomycin and teicoplanin. The lipopeptide daptomycin was included when it became available.

Dalbavancin had potent activity against the major classes of organisms included in the surveillance study. Its potency was maintained from 2002 through 2012, with no shifts in MIC distribution. The following tables summarize the MIC distribution in each year for US isolates of different organisms; the majority of the data, as well as the most recent available data, are for strains isolated in the US.

Trends in Dalbavancin Potency in the US

The MIC_{50} of dalbavancin for *S. aureus* was constant at 0.06 µg/mL during each year of the study; the MIC_{90} was also 0.06 µg/mL in 8 of the 11 years of the study (including 2010-2012) and was 0.12 µg/mL for isolates from the other 3 years. The MIC distributions, by year, for a total of nearly 40,000 *S. aureus* isolates are presented in Table 47.

Table 47 Eleven-Year (2002-2012) Surveillance Trends in Dalbavancin Potency against *S. aureus* from the USA

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2002 (1817)	579	1194	39	4	1	0.06	0.06
2003 (1326)	646	655	23	2	--	0.06	0.06
2004 (2442)	1095	1301	42	3	1	0.06	0.06
2005 (3618)	1369	2127	119	3	--	0.06	0.06
2006 (5713)	2074	3409	216	13	1	0.06	0.06
2007 (6111)	819	4663	612	17	--	0.06	0.12
2008 (5610)	519	4218	835	38	--	0.06	0.12
2009 (4990)	504	3775	660	51	--	0.06	0.12
2010 (6161)	2354	3592	195	20	--	0.06	0.06
2011 (1036)	391	611	32	2	--	0.06	0.06
2012 (1000)	192	716	91	1	--	0.06	0.06
All (39,824)	10,542 (26.5)[a]	26,261 (65.9)	2,864 (7.2)	154 (0.4)	3 (<0.1)	0.06	0.06

[a] Percentage of all strains in parenthesis.

Data from R. Jones, JMI Laboratories, SENTRY database.

More than half of the *S. aureus* surveillance isolates from the US were methicillin-resistant. Data for the MSSA and MRSA subsets are presented in Table 48 and Table 49, respectively. The dalbavancin MIC distributions over time are the same for MSSA and MRSA.

Table 48 Eleven-Year (2002-2012) Surveillance Trends in Dalbavancin Potency Against Methicillin-Susceptible *S. aureus* from the USA

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2002 (986)	298	663	23	2	--	0.06	0.06
2003 (843)	402	428	12	1	--	0.06	0.06
2004 (1232)	558	653	20	1	--	0.06	0.06
2005 (1765)	670	1042	53	--	--	0.06	0.06
2006 (2506)	934	1464	103	5	--	0.06	0.06
2007 (2711)	371	2038	294	8	--	0.06	0.12
2008 (2411)	256	1780	363	12	--	0.06	0.12
2009 (2441)	249	1855	312	25	--	0.06	0.12
2010 (3025)	1211	1707	99	8	--	0.06	0.06
2011 (514)	193	304	15	2	--	0.06	0.06
2012 (500)	108	350	42	--	--	0.06	0.06
All (18,934)	5,250 (27.7)[a]	12,284 (64.9)	1,336 (7.1)	64 (0.3)	--	0.06	0.06

[a] Percentage of all strains in parenthesis.

Data from R. Jones, JMI Laboratories, SENTRY database.

Table 49 Eleven-Year (2002-2012) Surveillance Trends in Dalbavancin Potency Against Methicillin-Resistant *S. aureus* from the USA

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2002 (831)	281	531	16	2	1	0.06	0.06
2003 (483)	244	227	11	1	--	≤0.03	0.06
2004 (1210)	537	648	22	2	1	0.06	0.06
2005 (1853)	699	1085	66	3	--	0.06	0.06
2006 (3207)	1140	1945	113	8	1	0.06	0.06
2007 (3400)	448	2625	318	9	--	0.06	0.06
2008 (3199)	263	2438	472	26	--	0.06	0.12
2009 (2549)	255	1920	348	26	--	0.06	0.12
2010 (3136)	1143	1885	96	12	--	0.06	0.06
2011 (522)	198	307	17	--	--	0.06	0.06
2012 (500)	84	366	49	1	--	0.06	0.06
All (20,890)	5,292 (25.3)[a]	13,977 (66.9)	1,528 (7.3)	90 (0.4)	3 (<0.1)	0.06	0.06

[a] Percentage of all strains in parenthesis.

Data from R. Jones, JMI Laboratories, SENTRY database.

The potency of dalbavancin against CoNS is very similar to what is reported for *S. aureus* (Table 50). Surveillance data for 7,016 CoNS isolates was collected during the 9-year period 2002-2010. In different years, the dalbavancin MIC_{50}s were either ≤ 0.03 or 0.06 µg/mL (0.06 µg/mL overall) and the MIC_{90}s were 0.06 or 0.12 µg/mL (overall, 0.12 µg/mL).

Table 50. Nine-Year (2002-2010) Surveillance Trends in Dalbavancin Potency against Coagulase-Negative Staphylococci from the USA

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)						MIC	
	≤0.03	0.06	0.12	0.25	0.5	1	50%	90%
2002 (335)	270	42	16	7	--	--	≤0.03	0.06
2003 (301)	208	66	18	6	3	--	≤0.03	0.06
2004 (305)	199	75	20	7	3	1	≤0.03	0.12
2005 (419)	272	113	25	6	2	1	≤0.03	0.06
2006 (1115)	662	350	77	23	2	1	≤0.03	0.06
2007 (1297)	482	613	167	32	2	1	0.06	0.12
2008 (1219)	387	604	189	36	3	--	0.06	0.12
2009 (1007)	313	510	157	22	4	1	0.06	0.12
2010 (1018)	612	328	74	3	1	--	≤0.03	0.06
All (7,016)	3,405 (48.5)[a]	2,701 (38.5)	743 (10.6)	142 (2.0)	20 (0.3)	5 (<0.1)	0.06	0.12

[a] Percentage of all strains in parenthesis.

Data from R. Jones, JMI Laboratories, SENTRY database.

Among the β-hemolytic streptococci tested, susceptibility data are presented for US isolates of *S. pyogenes* (N=2,051, Table 51) and *S. agalactiae* (N=2,700, Table 52. These organisms are highly susceptible to dalbavancin. The dalbavancin MIC_{50} was consistently ≤ 0.03 µg/mL for both species. The MIC_{90} for *S. pyogenes* was also ≤ 0.03 µg/mL. The overall dalbavancin MIC_{90} for *S. agalactiae* of 0.06 µg/mL was also the MIC_{90} in the most recent year of the study (2012).

Smaller numbers of representatives of other groups of β-hemolytic streptococci have also been tested. The susceptibility of these organisms to dalbavancin was comparable to that of the Group A and Group B streptococci (R. Jones 2011b).

Table 51 Eleven-Year (2002-2012) Surveillance Trends in Dalbavancin Potency against *S. pyogenes* from the USA

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2002 (31)	30	0	1	--	--	≤0.03	≤0.03
2003 (44)	44	--	--	--	--	≤0.03	≤0.03
2004 (95)	93	2	--	--	--	≤0.03	≤0.03
2005 (141)	141	--	--	--	--	≤0.03	≤0.03
2006 (225)	222	2	1	--	--	≤0.03	≤0.03
2007 (217)	214	3	--	--	--	≤0.03	≤0.03
2008 (187)	185	2	--	--	--	≤0.03	≤0.03
2009 (327)	317	10	--	--	--	≤0.03	≤0.03
2010 (478)	465	12	1	--	--	≤0.03	≤0.03
2011 (155)	143	11	1	--	--	≤0.03	≤0.03
2012 (151)	145	5	1	--	--	≤0.03	≤0.03
All (2,051)	1,999 (97.5)[a]	47 (2.3)	5 (0.2)	--	--	≤0.03	≤0.03

[a] Percentage of all strains in parenthesis.

Data from R. Jones, JMI Laboratories, SENTRY database.

Table 52 Eleven-Year (2002-2012) Surveillance Trends in Dalbavancin Potency against *S. agalactiae* from the USA

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2002 (61)	48	7	6	--	--	≤0.03	0.06
2003 (69)	63	5	1	--	--	≤0.03	≤0.03
2004 (118)	100	17	1	--	--	≤0.03	0.06
2005 (157)	151	4	0	2	--	≤0.03	≤0.03
2006 (275)	253	17	3	2	--	≤0.03	≤0.03
2007 (286)	258	25	3	--	--	≤0.03	≤0.03
2008 (238)	219	15	4	--	--	≤0.03	≤0.03
2009 (485)	382	68	28	7	--	≤0.03	0.06
2010 (724)	572	95	35	22	--	≤0.03	0.06
2011 (153)	78	41	20	14	--	≤0.03	0.12
2012 (134)	118	11	3	2	--	≤0.03	0.06
All (2,700)	2,242 (83.0)[a]	305 (11.3)	104 (3.9)	49 (1.8)	--	≤0.03	0.06

[a] Percentage of all strains in parenthesis.

Data from R. Jones, JMI Laboratories, SENTRY database.

From 2002 through 2010, nearly 2,000 viridans group streptococci from the US were included in the dalbavancin surveillance database. The overall dalbavancin $MIC_{50/90}$ for this organism group was 0.06 µg/mL.

7.2.3 Comparison of Overall Susceptibility to Dalbavancin in Europe and the US

Between 2002 and 2010, approximately 51,500 isolates from Europe were included in the dalbavancin surveillance database, for a total of nearly 124,000 strains when combined with US data collected over the same period for the major groups of aerobic Gram-positive cocci. As shown in the series of MIC distribution tables for US isolates, MIC distributions have remained consistent over time. This is also the case for European isolates; an example comes from analysis of staphylococcal and β-hemolytic streptococcal isolates collected from 5 countries in 2007 (Biedenbach 2009a), and from MIC distributions for key pathogen isolates from Europe, collected in 2006-2009 (Table 53, Jones 2011a)

Table 53 Dalbavancin Susceptibility of Key Pathogens Collected in European Hospitals from 2006 to 2009.

Organism (N)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	≥0.5	50%	90%
S. aureus (11,658)	2,773	7,987	863	35	0	0.06	0.06
MRSA (3,183)	914	2,018	238	13	0	0.06	0.06
MSSA (8,475)	1,859	5,969	625	22	0	0.06	0.06
β-hemolytic streptococci							
All (1,997)	1,893	85	15	4	0	≤0.03	≤0.03
S. pyogenes (793)	781	10	1	1	0	≤0.03	≤0.03
S. agalactiae (817)	740	61	12	3	0	≤0.03	≤0.03
Viridans streptococci (845)	744	95	6	0	0	≤0.03	0.06
Enterococcus spp.							
Van-S (4,457)	1,412	2,301	655	80	9	0.06	0.12
Van-R (525)	18	58	38	10	401	4	>4

Data from Jones 2011a.

Dalbavancin susceptibility data for US and European isolates collected from 2002 through 2010 are summarized in Table 54. Dalbavancin MIC values were ≤ 0.25 µg/mL for all groups of staphylococci and streptococci, and for ≥ 96% of *E. faecalis* isolates in both geographic regions; the exception was *E. faecium*, for which the vancomycin resistance rate was much higher among US than European isolates. There were no differences in the MIC_{90}s between the US and Europe for any group of organisms and essentially no difference in the MIC ranges. The MIC_{50}s of dalbavancin were also identical or comparable for all organisms except *E. faecium*.

Table 54. Summary of Nine-Year (2002-2010) Surveillance of Dalbavancin Potency against 7 Organism Groups: Comparison of US and European Susceptibility Data

Organism (No. Tested, USA/EU)	MIC (US/EU) in µg/mL			% (US/EU) at MIC (µg/mL)		
	50%	90%	Range	≤0.25	≤0.5	≤1
S. aureus (37,788/22,371)	0.06/ 0.06	0.06/ 0.06	≤0.03-0.5/ ≤0.03-0.5	>99.9/ >99.9	100.0/ 100.0	100.0/ 100.0
CoNS (7,016/7,947)	0.06/ ≤0.03	0.12/ 0.12	≤0.03-1/ ≤0.03-2	99.6/ 99.6	>99.9/ >99.9	100.0/ >99.9
β-HS (4,158/3,424)	≤0.03/ ≤0.03	≤0.03/ ≤0.03	≤0.03-0.25/ ≤0.03-0.25	100.0/ 100.0	100.0/ 100.0	100.0/ 100.0
VGS (1,974/1,862)	0.06/ 0.06	0.06/ 0.06	≤0.03-0.25/ ≤0.03-0.12	100.0/ 100.0	100.0/ 100.0	100.0/ 100.0
S. pneumoniae (9,503/7,837)	≤0.03/ ≤0.03	≤0.03/ ≤0.03	≤0.03-0.25/ ≤0.03-0.25	100.0/ 100.0	100.0/ 100.0	100.0/ 100.0
E. faecalis (7,456/5,653)	0.06/ 0.06	0.06/ 0.06	≤0.03->4/ ≤0.03->4	96.2/ 98.9	96.3/ 98.9	96.4/ 98.9
E. faecium (3,990/2,851)	4/ 0.06	>4/ >4	≤0.03->4/ ≤0.03->4	29.4/ 81.7	32.2/ 82.7	35.7/ 83.9

Data from R. Jones, JMI Laboratories, SENTRY database.
Abbreviations: CoNS=Coagulase-negative staphylococci; β-HS=β-hemolytic streptococci; VGS=Viridans group streptococci.

Smaller numbers of isolates from Canada, Latin America, and the Asia-Pacific region were included in some years of the study (data not shown). In 2006-2009, there were 11,692 staphylococcal isolates from Asia-Pacific and 6,711 from Latin America (Jones 2011a), and several thousand more isolates from each of these regions in earlier years, including streptococci (β-hemolytic and viridans group) and enterococci (Gales 2005, Biedenbach 2009b). The overall dalbavancin susceptibility patterns were the same when these data were included in the analysis.

7.2.4 Dalbavancin Potency Compared With Other Antimicrobial Agents

The following tables compare the activity of dalbavancin and other agents vs. US surveillance isolates. For comparators, the percent susceptibility, intermediate susceptibility and resistance according to US (CLSI) and European (EUCAST) criteria are included, when available. Similar comparative data has been published for surveillance isolates (2002-2010) from Europe and other regions (Jones 2005, Biedenbach 2009a, Biedenbach 2009b, Streit 2004, Jones 2011a).

Susceptibility data for β-hemolytic streptococci (which were mainly *S. pyogenes* and *S. agalactiae*) are in Table 55. Dalbavancin had greater potency against these organisms than the comparators, with the exception of penicillin, which had a similar MIC range. Significant resistance was observed for erythromycin (30.4%), clindamycin (14.9%) and tetracycline (> 50%).

Table 55 Comparative Activity of Dalbavancin Against 4,802 Isolates of β-Hemolytic Streptococci From the US (2002-2012)

Antimicrobial Agent	MIC (µg/mL)			%S /%I / %R[a]	
	50%	90%	Range	CLSI	EUCAST
Dalbavancin	≤0.03	0.06	≤0.03–0.25	- / - / -	- / - / -
Vancomycin	0.5	0.5	≤0.12 – 1	100.0 / - / -	100.0 / 0.0 / 0.0
Penicillin	≤0.06	≤0.06	≤0.06–0.25	>99.9 / - / -	100.0 / 0.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25–2	99.9 / - / -	100.0/<0.1/0.0
Erythromycin	≤0.25	>2	≤0.25–>2	68.9/0.7/30.4	68.9 / 0.7 / 30.4
Clindamycin	≤0.25	>2	≤0.25–>2	84.7/0.4/14.9	85.1 / 0.0 / 14.9
Daptomycin	≤0.12	0.25	≤0.12–0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Levofloxacin	≤0.5	1	≤0.5 – >4	99.1 / 0.1 / 0.8	96.0 / 3.1 / 0.9
Linezolid	1	1	≤0.12 – 2	100.0 / - / -	100.0 / 0.0 / 0.0
Tetracycline	>8	>8	≤4 – >8	45.1 / 1.5 / 53.4	44.9 / 0.2 / 54.9
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	- / - / -	98.5 / 0.4 / 1.1

Abbreviations: S=Susceptible; I=Intermediate; R=Resistant;
TMP/SMX=trimethoprim/sulfamethoxazole.

[a] Criteria as published by CLSI (2013) and EUCAST (2013)

Data from R. Jones, JMI Laboratories, SENTRY database.

On the basis of MIC range, dalbavancin had more potent activity than the comparators against *S. pneumoniae* (Table 56). Low frequencies of resistance were exhibited by vancomycin, ceftriaxone, levofloxacin and linezolid. A greater extent of resistant was seen with penicillin, erythromycin, clindamycin, tetracycline and trimethoprim/sulfamethoxazole.

Table 56 Comparative Activity of Dalbavancin Against 9,503 Isolates of *S. pneumoniae* From the US (2002-2010[a])

Antimicrobial Agent	MIC (µg/mL)			%S /%I / %R[b]	
	50%	90%	Range	CLSI	EUCAST
Dalbavancin	≤0.03	≤0.03	≤0.03 – 0.25	- / -/ -	- / -/ -
Vancomycin	≤1	1	≤1 – 1	100.0 / -/ -	100.0 / 0.0 / 0.0
Penicillin	≤0.03	4	≤0.03 – >4	61.6 / 19.6 / 18.8[b]	61.6 / 26.9 / 11.5
Ceftriaxone	≤0.25	1	≤0.25 – 16	92.9 / 5.5 / 1.6	82.4 / 16.0 / 1.6
Erythromycin	≤0.25	>2	≤0.25 – >2	64.9 / 0.6 / 34.5	64.9 / 0.6 / 34.5
Clindamycin	≤0.25	>1	≤0.25 – >1	82.9 / 0.4 / 16.7	83.3 / 0.0 / 16.7
Levofloxacin	1	1	≤0.5 – >4	99.2 / 0.1 / 0.7	99.2 / 0.0 / 0.8
Linezolid	1	1	≤0.25 – 4	>99.9 / -/ -	100.0 / 0.0 / 0.0
Tetracycline	≤4	>8	≤4 – >8	78.4 / 1.0 / 20.6	78.4 / <0.1 / 21.6
TMP/SMX	≤0.5	>2	≤0.5 – >2	68.5 / 7.8 / 23.7	73.6 / 2.7 / 23.7

Abbreviations: S=Susceptible; I=Intermediate; R=Resistant;
TMP/SMX=trimethoprim/sulfamethoxazole.

[a] Criteria as published by CLSI (2013) and EUCAST (2013)

[b] Criteria as published by CLSI (2013) for oral penicillin V (S/I/R=≤0.06/0.12-1/≥2 µg/mL.

Data from R. Jones, JMI Laboratories, SENTRY database.

7.2.5 European Surveillance Study

Unique patient isolates (N=1008) of staphylococci and β-hemolytic streptococci were collected in 2011-2012 from hospitals across Europe; sources were largely (approximately 86%) skin/wound, bacteremia and respiratory infections (Deane 2012; data on file). MIC determinations were by broth microdilution with addition of P-80. Among 756 *S. aureus* isolates, 179 (24%) were MRSA; 65 (69%) of the 94 coagulase-negative staphylococci were methicillin-resistant. Among 158 β-hemolytic streptococci, there were 74 *S. pyogenes*, 76 *S. agalactiae* and 8 Group C or G isolates. Dalbavancin susceptibility data (MIC_{90}s), in comparison with vancomycin, daptomycin and linezolid, are summarized in Table 57. Dalbavancin had more potent activity than vancomycin, daptomycin or linezolid; dalbavancin MIC_{90} values were lower than those of non-β-lactam comparators (N=9 for staphylococci and 8 for streptococci) by factors of 4- to 32-fold against the staphylococci and 4- to > 128-fold against the streptococci. Susceptibility to dalbavancin among these organisms was similar to what was seen in the SENTRY and other surveillance studies.

Table 57 Activity of Dalbavancin and Selected Comparators against European Isolates of Staphylococci and β-Hemolytic Streptococci

Organism	N	MIC_{90} (µg/mL)			
		Dalbavancin	Vancomycin	Daptomycin	Linezolid
S. aureus	756	0.06	1	0.5	2
CoNS	94	0.12	2	1	2
BHS	158	0.03	0.5	0.25	1

Abbreviations: CoNS=Coagulase-negative staphylococci; BHS=β-hemolytic streptococci (including 74 *S. pyogenes*, 76 *S. agalactiae*, 1 Group C, and 7 Group G streptococci).

7.2.6 Other Surveillance Studies

Other surveillance studies include assessment of relevant staphylococcal and streptococcal isolates from sites in Canada, Belgium and Korea, with results of similar outcome than the other major surveillance programs in the United States and Europe.

7.2.6.1 In Vitro Activity of Dalbavancin against Bacteria Resistant to Other Classes of Antimicrobial Agents or with Reduced Susceptibility to Glycopeptides

The surveillance and other studies discussed above included thousands of isolates of Gram-positive cocci with resistance phenotypes commonly encountered in the clinic. Among organisms causing ABSSSI, MRSA is the most frequently encountered resistance phenotype. MRSA are highly prevalent worldwide and are usually resistant to multiple antibiotic classes including fluoroquinolones and clindamycin. The potent activity of dalbavancin against MRSA (equivalent to its activity against methicillin-susceptible staphylococci) was demonstrated against tens of thousands of clinical isolates in a number of studies, principally the SENTRY data base (Section 7.2.2). These isolates were largely from skin and other serious infections, and from hospitals worldwide, in particular from the US and Europe. Potent activity of dalbavancin against erythromycin-resistant *S. pyogenes*, as well as β-lactam-resistant streptococci (pneumococci and viridans group streptococci) was also demonstrated in several of these studies. Other studies were designed to challenge dalbavancin by testing its activity against more novel resistance phenotypes (eg, to more recently introduced antimicrobial agents) and against MDR isolates.

U.S. and European SENTRY database (2002-2012)

Among this large set of isolates, 52.5% of the *S. aureus* isolates and 74.1% of the CoNS were MR, based on oxacillin MIC data. By CLSI criteria, there were no glycopeptide-resistant or -intermediate *S. aureus* isolates, although by EUCAST criteria there were a small number of isolates with intermediate susceptibility to vancomycin (< 0.1%) or teicoplanin (0.3%). The highest dalbavancin MIC was 0.5 µg/mL (for < 0.1% of *S. aureus* isolates; see Table 47. Among the CoNS isolates, there were no vancomycin-R isolates and very few (0.3%) teicoplanin-R isolates by CLSI criteria. By EUCAST criteria, although vancomycin resistance was rare (0.1%), 9.8% of CoNS isolates were categorized as teicoplanin-R. The highest dalbavancin MIC for CoNS isolates was 1 µg/mL; <0.4% of isolates had dalbavancin

MIC results of 0.5-1 µg/mL (see Table 50 in Section 7.2.2). A number of reports focused specifically on resistant isolates from worldwide sources.

Eurofins-Medinet (Pillar 2011; Data on File)

A study was performed to evaluate the *in vitro* activity of dalbavancin against isolates non-susceptible to current anti-staphylococcal therapies. Forty-two clinical isolates of *S. aureus* previously characterized as non-susceptible to linezolid (n=11), daptomycin (n=21), and tigecycline (n=10) were evaluated for susceptibility to dalbavancin and comparators by broth microdilution per CLSI M7-A8 and M100-S21; the minimum bactericidal concentration (MBC) for dalbavancin was also evaluated per CLSI M26-A.

Confirmation of daptomycin and tigecycline non-susceptibility and linezolid resistance was determined for the isolates described in Table 58. Dalbavancin had potent in vitro activity against the evaluated *S. aureus* consisting of isolates non-susceptible to currently available and commonly utilized agents, with lower MICs than comparator glycopeptides (vancomycin/teicoplanin) and the lipopeptide daptomycin.

Table 58. Activity of Dalbavancin *In vitro* against *S. aureus* Resistant to Currently-Utilized Anti-MRSA Therapeutics[a]

	QC strain of *S. aureus* (ATCC 29213)			
	MIC	mode	MIC_{50}	MIC_{90}
Dalbavancin	0.03	NA		
Vancomycin	1			
Oxacillin	0.25			
	Daptomycin non susceptible (n=18)			
	range	mode	MIC_{50}	MIC_{90}
Dalbavancin	0.03-0.5	0.06	0.06	0.5
Vancomycin	1-8	2	2	8
Oxacillin	0.12 - >4	> 4	> 4	> 4
	Linezolid resistant (n=9)			
	range	mode	MIC_{50}	MIC_{90}
Dalbavancin	0.03-0.06	0.03	NA	NA
Vancomycin	0.5-2	1	NA	NA
Oxacillin	2 - > 4	> 4	NA	NA
	Tigecycline non-susceptible (n=7)			
	range	mode	MIC_{50}	MIC_{90}
Dalbavancin	0.03-0.06	0.03	NA	NA
Vancomycin	1-1	1	NA	NA
Oxacillin	> 4 - > 4	> 4	NA	NA

[a] All susceptibility values are expressed in µg/mL
Abbreviation: NA=not applicable

7.3 Bactericidal Activity of Dalbavancin

Dalbavancin is bactericidal for target organisms *in vitro* at concentrations of free drug that are sustained in human plasma throughout the one-week dosing interval. Dalbavancin is more consistently bactericidal than vancomycin or teicoplanin. Studies of the bactericidal activity of dalbavancin have included determination of minimal bactericidal concentration (MBC) and time kill experiments. The in vitro bactericidal activity of dalbavancin is time-dependent, similarly to conventional glycopeptides such as vancomycin and teicoplanin. Dalbavancin has also shown bactericidal activity in animal infection models.

7.3.1 Minimal Bactericidal Concentration (MBC)

The MBC is a rapid method for estimating bactericidal activity, because it consists of simply plating the contents of clear wells after MIC determination by the broth microdilution method. The MBC is usually arbitrarily defined as the lowest concentration of an antibiotic needed to kill 99.9% of viable organisms after exposure for 24 hours. The accuracy of this method is limited because of the low number of CFU on which it is based; in some cases presence or absence of one or a few colonies may determine the MBC. Based on the Poisson distribution, statistical tables of cut-off values for 99.9% kill (based on pipetting errors, inoculum and sample size) have been published (Pearson 1980), but these corrections are rarely applied in practice; therefore, on average, the percent kill may be under-estimated and thus the MBC may be over-estimated.

In the case of dalbavancin, adherance to plastic surfaces is an issue, as in MIC determination. Studies in which precautions have been taken to ensure solubility and to prevent dalbavancin from adhering to plastic surfaces demonstrated dalbavancin MBC values to be close to the MIC values for most staphylococcal and streptococcal isolates tested. As discussed above, the methodology utilized may tend to inflate the MBC values; the extent of the error might be higher for agents having time-dependent bactericidal activity.

There is variability in MBC/MIC ratios among strains of the same species in the absence of P-80. There is a trend toward higher ratios at lower MIC values. This may be because longer exposure of dalbavancin to plastic in the absence of P-80 leads to progressive loss of dalbavancin activity from solution (Rennie 2007), which might lead to some re-growth. The fraction of dalbavancin lost from solution is higher when the initial concentration is lower.

7.3.2 Time Kill Studies

Time-kill studies generally utilize a higher inoculum, which provides a more reliable estimate of the extent of bacterial killing than in MBC determinations. The bactericidal activity of dalbavancin was also assessed in several time-kill studies (Candiani 1999, Jones 2001, Bozdogan 2003, Lopez 2005, Lin 2005a, Lin 2005b).

Dalbavancin is bactericidal for target organisms at concentrations that are sustained in human plasma over the dosing interval with proposed regimens. Results were similar in experiments based on total drug concentrations in the presence of 50% human serum, and in experiments using estimated unbound drug concentrations in the absence of serum. Using concentrations

spanning estimated unbound dalbavancin concentrations, time-dependent bactericidal activity was observed.

In general, just as MICs are about 4-fold lower when appropriate conditions are used to ensure its in vitro availability, killing by dalbavancin is observed at lower concentrations when using either a wetting agent (in time-kill experiments) or dry-form microtiter trays (for MBC determination).

7.4 Clinical Isolates With Decreased Susceptibility to Dalbavancin

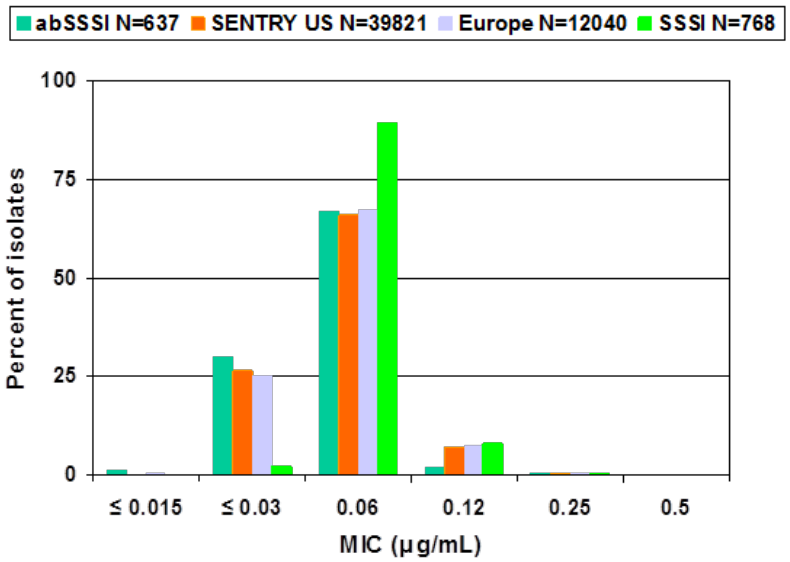
An MIC frequency distribution was previously constructed using dalbavancin MIC values from 5 dalbavancin clinical efficacy studies (VER001-4, VER001-5, VER001-8, VER001-9 and VER001-16) and a number of surveillance studies and other laboratory studies. These data are supplemented with results from the ABSSSI clinical trials and from an 11-year surveillance studies (with data available through 2012).

7.4.1 MIC Distributions for *S. aureus*

7.4.1.1 ABSSSI Studies

As shown in Figure 28, the dalbavancin MIC distributions for the baseline isolates from the ABSSSI trials and more recent U.S. (SENTRY 2002-2012) and European (SENTRY 2006-2009, Jones 2011a; 2011-2012, Deane 2012) surveillance data, are consistent with the data from the 4 cSSSI and uSSSI studies. This is not surprising, as the MIC distributions for surveillance isolates in the SENTRY study have not varied from 2002 through 2012 (Section 7.2.2). Additional *S. aureus* isolates collected in Europe (more than 22,000 total from 2002 through 2010) show the same MIC range, MIC_{50} and MIC_{90} as the nearly 38,000 US isolates collected during the same period (Table 54). Together, the US surveillance data for 2002-2012 and the European data for 2002-2010 comprise > 60,000 *S. aureus* isolates. The MIC values are distributed in a unimodal manner, ranging from ≤0.015 to 0.25 µg/L in the clinical studies and ≤ 0.03 to 0.5 µg/mL in the SENTRY study. For *S. aureus* the MIC_{50} and MIC_{90} of dalbavancin in both clinical and surveillance studies are 0.06 µg/mL. There are a few isolates at MIC 0.25 µg/ml and a smaller number at 0.5 µg/mL. Because the lowest concentration of dalbavancin reported in the SENTRY data is 0.03 µg/mL, this distribution appears truncated on the lower end; however it is clear that the MIC distributions are superimposable and consistent over time for both clinical trial and surveillance isolates.

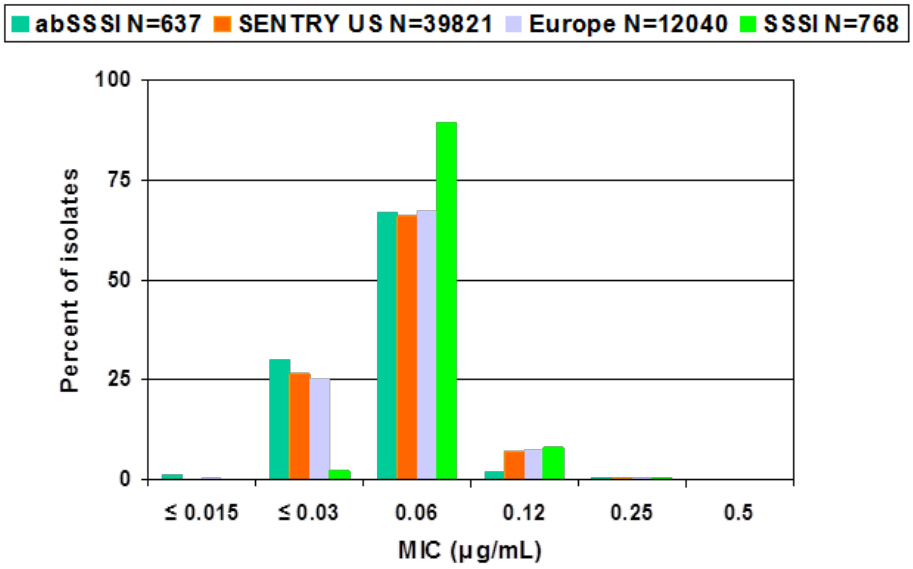
Figure 28 Dalbavancin MIC Distributions: *S. aureus* From Clinical Trial (ABSSSI and SSSI Baseline Isolates) and Surveillance Studies



Source: R. Jones, JMI Laboratories, SENTRY database; Deane 2012; Jones 2011a; IHMA Database

Dalbavancin MIC distributions of dalbavancin for isolates from both clinical trials and surveillance studies were the same for the MRSA subsets as for all *S. aureus* (Figure 29).

Figure 29 Dalbavancin MIC Distribution: MRSA From Clinical Trial (ABSSSI and SSSI Baseline Isolates) and Surveillance Studies



Source: R. Jones, JMI Laboratories, SENTRY database; Deane 2012; Jones 2011a; IHMA Database

7.4.2 MIC Determinations for *Streptococcus* spp.

7.4.2.1 Clinical Trials Performed Prior to 2005

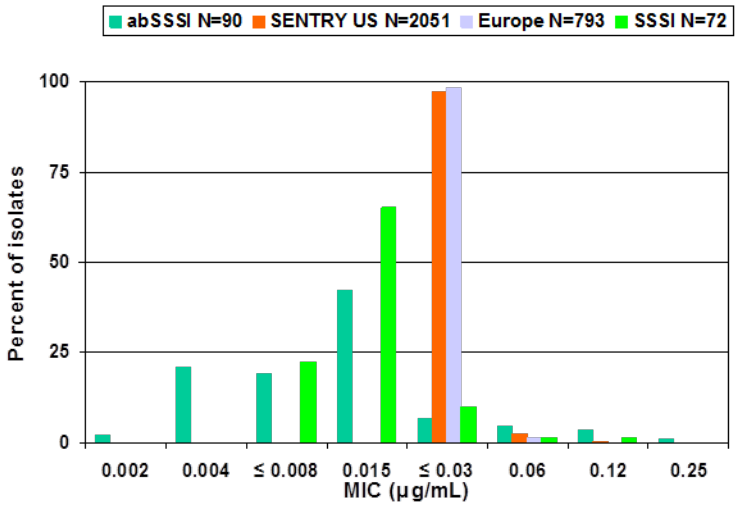
The distribution of dalbavancin MIC values for *Streptococcus* spp. from the early clinical studies (n=173) was similar to that of isolates from surveillance studies then available (n=1231) (Figure 30). The distributions were unimodal with MIC values from ≤ 0.015 to 0.12 µg/mL and ≤ 0.015-0.25 µg/mL for the clinical trial and surveillance isolates, respectively.

7.4.2.2 ABSSSI Studies

Figure 30 shows the dalbavancin MIC distributions for *S. pyogenes* ABSSSI surveillance isolates from the U.S. (2002-2012) and Europe (2006-2009 SENTRY, Jones 2011a; 2011-2012, Deane 2012) as compared with results from the cSSSI and uSSSI clinical trials.

MIC distributions for β-hemolytic streptococci overall were similar for isolates from Europe (n=3,424) and the U.S. (n=4,158) collected from 2002-2010 (Table 54).

Figure 30 Dalbavancin MIC Distributions: *S. pyogenes* From Clinical Trial (ABSSSI and SSSI Baseline Isolates) and Surveillance Studies

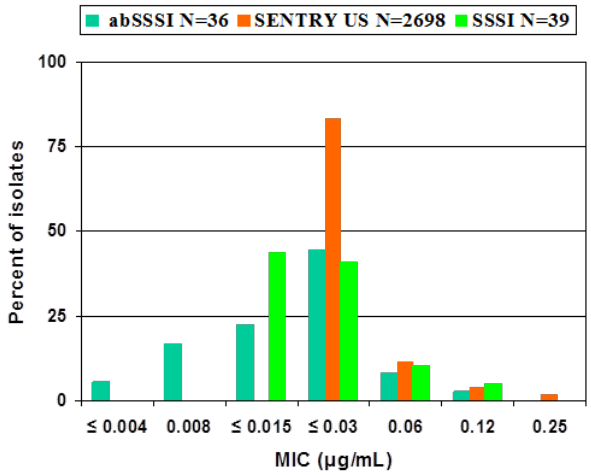


Source: R. Jones, JMI Laboratories, SENTRY database; Jones 2011a; IHMA Database

Although the numbers are smaller, distributions are also available for *S. agalactiae* and *S. anginosus* group streptococci.

Figure 31 compares baseline clinical isolates of *S. agalactiae* from the ABSSSI studies, the 4 SSSI studies and U.S. surveillance data. There is some skewing of the surveillance data, as 0.03 µg/mL was the lowest concentration of dalbavancin tested in that study.

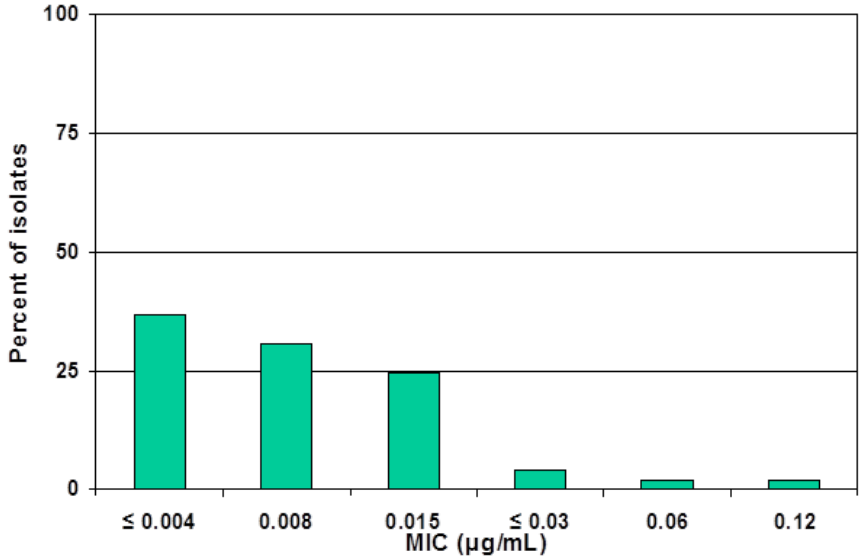
Figure 31 Dalbavancin MIC Distributions: *S. agalactiae* From Clinical Trial (ABSSSI and SSSI Baseline Isolates) and Surveillance Studies



Source: R. Jones, JMI Laboratories, SENTRY database; IHMA Database

Data for baseline isolates of *S. anginosus* group streptococci from the ABSSSI clinical trials are shown in Figure 32. Surveillance data are available only for unspeciated viridans streptococci.

Figure 32 Dalbavancin MIC Distribution: *S. anginosus* Group Isolates From the ABSSSI Clinical Trials



7.5 Proposed Breakpoints

Based on the results of *in vitro* testing, animal studies, PK/PD modeling, surveillance programs and clinical trial data, the provisional breakpoint for susceptibility to dalbavancin of Gram-positive bacteria, including MSSA and MRSA, submitted for review in

NDA 021-883 is ≤0.25 µg/mL. PK/PD data and results recent ABSSSI studies support this value as an appropriate susceptibility breakpoint for both staphylococci and streptococci. As dalbavancin MICs have remained clustered at 0.03-0.06 µg/ml, with few isolates at 0.12 - 0.25 µg/mL, and with clinical outcomes consistently high across all MIC determinations, the MIC threshold at which clinical failure is more likely to occur has not been identified. In the absence of any clinical data suggesting an appropriate breakpoint for resistance, clinical isolates with higher MICs might be better termed 'non-susceptible.'

Monte Carlo simulations were performed based on a number of factors. These included the MIC distributions and eradication rates for *S. aureus* and streptococci in the phase 3 cSSSI and uSSSI clinical trials and the population PK of dalbavancin in patients. Because of the narrow range of MICs encountered in clinical studies and among surveillance isolates, wider MIC distributions were modeled based on PD considerations from the neutropenic mouse thigh model. These animal experiments demonstrated a relationship between efficacy and the ratio of free drug AUC to MIC for *S. aureus* and *S. pneumoniae*. However, an additional consideration was the observation that plasma levels of free dalbavancin almost always exceeded the MIC throughout the course of the experiments, as is also seen in human plasma throughout the treatment period with the proposed dosages. The binding of dalbavancin to protein in human and mouse plasma was taken into account in the modeling. Another consideration is that bactericidal concentrations of free dalbavancin are maintained over the entire treatment period in individuals receiving the proposed dosage. These analyses support a susceptibility interpretive criterion for dalbavancin of ≤ 0.25 µg/mL

8 CLINICAL SAFETY

8.1 DEMOGRAPHIC AND OTHER CHARACTERISTICS OF STUDY POPULATION

8.1.1 Demographic and Baseline Characteristics

Overall, the demographic and Baseline characteristics were similar between dalbavancin and comparator groups and amongst the phase 1, phase 2/3, and, at the request of the Agency, phase 3 DUR001-301/302 integrated analysis sets (Table 59). Demographics and Baseline characteristics including age, gender, race, height, weight, body mass index (BMI), and CL_{Cr} were summarized by treatment group for each of the 3 groups of studies. Baseline characteristics of patients in phase 2/3 studies were summarized previously (Section 6.2.3) and are repeated in this section for completeness.

All treatment groups included approximately equal proportions of male and female subjects, and the majority of subjects were White and < 65 years of age. The mean ages between dalbavancin and comparator groups were similar in the phase 1 (35.8 vs. 27.8 years), phase 2/3 (48.3 vs. 49.2 years), and phase 3 DUR001-301/302 (48.9 vs. 50.3 years) integrated analysis sets. The mean proportion of subjects that were ≥ 65 years of age ranged between 16.3% and 19.0% for subjects in the phase 2/3 and phase 3 DUR001-301/302 integrated analysis sets. The mean BMI between dalbavancin and comparator groups were similar in the phase 1 (25.7 vs. 24.9 kg/m^2), phase 2/3 (29.9 vs. 29.4 kg/m^2), and phase 3 DUR001-301/302 (29.2 vs. 29.1 kg/m^2) integrated analysis sets.

Table 59 Demographic and Baseline Characteristics: Safety Population

	Phase 1 Integrated Analysis Set		Phase 2/3 Integrated Analysis Set		Phase 3 DUR001-301/302 Integrated Analysis Set	
	Dalbavancin (N=286)	Comparator (N=122)	Dalbavancin (N=1778)	Comparator (N=1224)	Dalbavancin (N=652)	Comparator (N=651)
Age (years)						
Mean (SD)	35.8 (15.42)	27.8 (8.49)	48.3 (16.44)	49.2 (16.51)	48.9 (16.03)	50.3 (15.73)
Median	31.0	25.0	47.0	49.0	49.0	51.0
Min, Max	12, 81	18, 54	16, 93	18 ,92	18, 85	18, 84
Age Group (years) N (%)						
< 65	269 (94.1)	122 (100.0)	1465 (82.4)	995 (81.3)	546 (83.7)	527 (81.0)
≥ 65	17 (5.9)	0 (0.0)	313 (17.6)	229 (18.7)	106 (16.3)	124 (19.0)
Gender N (%)						
Male	138 (48.3)	61 (50.0)	1066 (60.0)	711 (58.1)	388 (59.5)	374 (57.5)
Female	148 (51.7)	61 (50.0)	712 (40.0)	513 (41.9)	264 (40.5)	277 (42.5)
Race N (%)						
White	209 (73.1)	100 (82.0)	1388 (78.1)	1008 (82.4)	587 (90.0)	578 (88.8)
Black or African American	40 (14.0)	7 (5.7)	143 (8.0)	88 (7.2)	28 (4.3)	35 (5.4)
Asian	23 (8.0)	7 (5.7)	36 (2.0)	41 (3.3)	27 (4.1)	32 (4.9)
American Indian or Alaska Native	2 (0.7)	4 (3.3)	5 (0.3)	4 (0.3)	5 (0.8)	4 (0.6)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)
Other	11 (3.8)	4 (3.3)	205 (11.5)	82 (6.7)	4 (0.6)	1 (0.2)
BMI (kg/m^2)						
Mean (SD)	25.7 (4.18)	24.9 (2.99)	29.9 (8.18)	29.4 (7.96)	29.2 (7.17)	29.1 (7.16)
Median	25.2	24.9	27.9	27.8	27.5	27.6
Min, Max	17, 41	16, 36	14, 98	14, 91	14, 69	17, 65
BMI (kg/m^2) Distribution N (%)						
Underweight (<18.5)	3 (1.0)	1 (0.8)	23 (1.3)	18 (1.5)	5 (0.8)	9 (1.4)
Normal Weight (≥ 18.5, <25.0)	136 (47.6)	62 (50.8)	465 (26.2)	359 (29.3)	177 (27.1)	203 (31.2)
Overweight (≥25)	147 (51.4)	59 (48.4)	1273 (71.6)	841 (68.7)	470 (72.1)	438 (67.3)

Abbreviations: BMI= body mass index, SD= standard deviation

8.2 Overall Extent of Exposure

The entire dalbavancin clinical development program consisted of a total of 3442 subjects, 2092 of whom were treated with dalbavancin, and 1350 of whom were treated with a comparator (1276 active comparator and 74 placebo). The number of subjects in the ITT populations for both the dalbavancin treatment group and the comparator treatment group in the completed studies in the clinical development program are provided in Table 60.

There were a total of 431 subjects (307 in the dalbavancin group, 50 in the comparator group, and 74 in the placebo group) in 14 phase 1 studies; a total of 136 patients (81 in the dalbavancin group and 55 in the comparator group) in 2 phase 2 studies; and 2875 patients (1704 in the dalbavancin group and 1171 in the comparator group) in 5 phase 3 studies.

The total study program population included 3431 adults and 11 adolescents. A total of 22 subjects had severe renal impairment, 26 subjects had mild or moderate renal impairment, and 27 subjects had mild, moderate, or severe hepatic impairment in the phase 1 studies.

The phase 2/3 integrated analysis set included a total of 2214 patients with ABSSSI/cSSSI (VER001-9, VER001-16 [30/107 in dalbavancin group and 18/31 in comparator group], DUR001-301, DUR001-302); 1260 who were assigned to receive dalbavancin and 954 subjects who were assigned to receive comparator. The phase 3 DUR001-301 and DUR001-302 ABSSSI studies, the core of the clinical database, included a total of 1312 patients: 659 patients who were assigned to receive dalbavancin and 653 patients who were assigned to receive comparator. Of the 2092 subjects treated with dalbavancin, 1785 were assigned to receive the proposed recommended therapeutic dose regimen (1000 mg on Day 1 and 500 mg on Day 8).

Table 60 Enumeration of Subjects for Dalbavancin Drug Development

Study Grouping Study Subgrouping Study	Dalbavancin	Dalbavancin Proposed Dose[a]	Active Comparator	Placebo	Total
Phase 1 studies	307	NA	50	74	431
Single-dose studies	238	NA	50	59	347
Multiple-dose studies	69	27	0	15	84
Phase 2 studies	81	54	55	0	136
Phase 3 studies	1704	1704	1171	0	2875
Phase 2 and Phase 3 studies[b]	1785	1758	1226	0	3011
Phase 3 DUR001-301 and DUR001-302 studies[c]	659	659	653	0	1312
Phase 1, Phase 2, and Phase 3 studies	2092	1785	1276	74	3442

[a] 1000 mg on Day 1 and 500 mg on Day 8
[b] For the ITT population; subjects in the safety population for the phase 2/3 integrated analysis set included 1778 dalbavancin-treated subjects and 1224 comparator-treated subjects.
[c] For the ITT population; subjects in the safety population for the phase 3 integrated analysis set included 652 dalbavancin-treated subjects and 651 comparator-treated subjects.

Abbreviation: NA = not applicable

8.3 Discontinuations from Treatment/Withdrawal from Study

Overall, the incidences of subjects who prematurely discontinued study drug or withdrew from the study and the reasons were similar between the phase 1 integrated analysis set, phase 2/3 integrated analysis set, and phase 3 DUR001-301/302 integrated analysis set. Most subjects in the phase 1, phase 2, and phase 3 studies completed study drug. The percentage of subjects who discontinued study drug was small and similar between the dalbavancin and comparator treatment groups in the phase 1 (2.1% vs. 0.8%), phase 2/3 (12.3% vs. 11.7%), and phase 3 (6.7% vs. 7.8%) integrated analysis sets, respectively (Table 61). The most common reasons for premature discontinuation of study drug were TEAEs, withdrawal of consent, and lost to follow up. Similar proportions of subjects across all studies and across treatment groups discontinued study drug due to a TEAE. In pivotal phase 3 studies DUR001-301 and DUR001-302, patients who discontinued from study drug were encouraged to remain in the study to complete safety evaluations and follow-up.

Table 61 Premature Discontinuation From Study Drug: Safety Population

	Phase 1 Integrated Analysis Set		Phase 2/3 Integrated Analysis Set		Phase 3 DUR001-301/302 Integrated Analysis Set	
	Dalbavancin (N=286)	Comparator (N=122)	Dalbavancin (N=1785)	Comparator (N=1226)	Dalbavancin (N=659)	Comparator (N=653)
Completed study drug	280 (97.9)	121 (99.2)	1518 (85.0)	1061 (86.5)	608 (92.3)	601 (92.0)
Prematurely discontinued from study drug	6 (2.1)	1 (0.8)	219 (12.3)	143 (11.7)	44 (6.7)	51 (7.8)
Reason for premature discontinuation of study drug						
Adverse Event	3 (1.0)	1 (0.8)	49 (2.7)	31 (2.5)	11 (1.7)	14 (2.1)
Treatment failure/worsening clinical status	0	0	25 (1.4)	16 (1.3)	8 (1.2)	8 (1.2)
Withdrew Consent	2 (0.7)	0 (0.0)	21 (1.2)	19 (1.5)	6 (0.9)	9 (1.4)
Lost to Follow Up	1 (0.3)	0 (0.0)	27 (1.5)	13 (1.1)	0	0
Death	0	0	0 (0.0)	1 (0.1)	0	0
Subject Non-Compliance	0	0	10 (0.6)	9 (0.7)	3 (0.5)	0 (0.0)
Withdrawn at Investigator's Discretion	0	0	6 (0.3)	9 (0.7)	0	0
Other	0	0	81 (4.5)	45 (3.7)	16 (2.4)	20 (3.1)

8.4 Summary of Adverse Events

8.4.1 Characteristics of Observed Adverse Events

In nonclinical studies, target organ toxicities included the kidney, liver and infusion site-associated reactions (Section 4.3). Based on animal toxicology data and the safety profile of this pharmacological class, renal, hepatic, and infusion site-associated AEs were closely evaluated in the clinical studies (Section 8.4.6). The development program was specifically designed with particular attention paid to laboratory monitoring as well as to AEs related to these organ systems.

Overall results of AE analyses from the phase 1 to phase 3 studies are described in Table 62. The major focus of the safety analysis in this briefing document will be on the phase 2/3 database. No protocol-defined dose-limiting toxicity was identified at weekly multiple dose

regimens up to 1600 mg in the phase 1 dose-ranging safety study, or up to cumulative weekly doses of up to 4500 mg for up to 8 weeks.

Table 62 Overview of Treatment-Emergent Adverse Events: Safety Population

	Phase 1 Integrated Analysis Set		Phase 2/3 Integrated Analysis Set		Phase 3 DUR001-301/302 Integrated Analysis Set	
Number (%) of Subjects with:	Dalbavancin (N=286)	Comparator (N=122)	Dalbavancin (N=1778)	Comparator (N=1224)	Dalbavancin (N=652)	Comparator (N=651)
Any TEAE	180 (62.9)	36 (29.5)	799 (44.9)	573 (46.8)	214 (32.8)	247 (37.9)
P value[a]			*0.012*		*0.053*	
Any Tx-related TEAE	99 (34.6)	21 (17.2)	328 (18.4)	246 (20.1)	80 (12.3)	89 (13.7)
P value[a]			*0.014*		*0.452*	
Any SAE	4 (1.4)	0	109 (6.1)	80 (6.5)	17 (2.6)	26 (4.0)
P value[a]			*0.266*		*0.161*	
Any Tx-related SAE	0	0	3 (0.2)	9 (0.7)	2 (0.3)	4 (0.6)
P value[a]			*0.021*		*0.412*	
Discontinuations from Study Drug Due to TEAE	4 (1.4)	1 (0.8)	53 (3.0)	35 (2.9)	14 (2.1)	13 (2.0)
P value[a]			*0.857*		*0.849*	
Withdrawals from Study Due to TEAE	0	0	17 (1.0)	6 (0.5)	0	0
P value[a]			*0.434*		*NA*	
Deaths	0	0	10 (0.6)	14 (1.1)	1 (0.2)	7 (1.1)
P value[a]			*0.087*		*0.033*	

[a] *P*-value is for Dalbavancin vs. Comparator and is from the Cochran-Mantel-Haenszel test of general association, stratified by study. *P* values were not calculated for the phase 1 integrated analysis set.

Note: Treatment-related AEs are defined as those reported as possibly or probably related to study treatment or AEs for which the relationship was missing. Adverse events with missing intensity are considered severe. For summarizations of number of subjects, subjects are only counted once; for number of AE summarizations, subjects may be counted multiple times, according to the number of AEs experienced. Percentages of total number of treatment-related AEs and SAEs are based on total number of AEs.
Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event, Tx=treatment

8.4.2 All Causality Adverse Events

Overall, the all-causality AE profile in the phase 2/3 dalbavancin-treated patients was similar to, or better than, that in comparator-treated patients. The incidence of patients in the phase 2/3 integrated analysis set experiencing at least 1 TEAE (44.9% vs. 46.8%; p=0.012), as well as the proportion of patients with at least 1 treatment-related TEAE (18.4% versus 20.1%; *P*= 0.014), was lower for the patients receiving dalbavancin relative to the patients receiving comparator (Table 63). In general, the percentages in the individual AE classifications in the overview profile were numerically lower for dalbavancin than for comparator drugs. There were no treatment-related deaths and few treatment-related SAEs. Most AEs were mild or moderate in intensity.

Table 63 Overview of Adverse Events, Phase 2/3 Integrated Database

Patients with:	Total Dalbavancin n = 1778	Total Comparator n = 1224
≥ 1 AE, n (%)	799 (44.9)	573 (46.8)
≥ 1 treatment-related AE, n (%)	328 (18.4)	246 (20.1)
≥ 1 SAE, n (%)	109 (6.1)	80 (6.5)
≥ 1 treatment-related, n (%)SAE	3 (0.2)	9 (0.7)
≥ 1 AE leading to discontinuation of study drug, n (%)	53 (3.0)	35 (2.9)
Number (%) deaths	10 (0.6)	14 (1.1)
Number (%) of deaths due to treatment-related AE	0	0

Abbreviations: AE = adverse event; SAE = serious adverse event

Adverse events were most commonly reported in the 'gastrointestinal disorders' system organ class (SOC). AEs in this SOC were reported by 15.5% of dalbavancin-treated patients and 16.5% of comparator-treated patients. In general, the frequency of AEs for both treatment groups was slightly higher in patients who received 2 weekly doses, or the equivalent of 14 days of treatment, compared with those who received 1 dose or the equivalent of 7 days of treatment. This outcome is most likely reflective of a greater severity of illness in patients treated with longer courses of therapy. Individual AE terms were often reported less frequently in patients treated with dalbavancin than in patients treated with a comparator drug.

Adverse events occurring in > 2% of dalbavancin treated patients are presented by order of decreasing frequency in Table 64. The 3 most commonly reported AEs for both treatment groups were nausea, diarrhea, and headache; these events were reported less frequently in dalbavancin-treated patients than in comparator-treated patients.

Table 64 Adverse Events Occurring in > 2% of Patients Receiving Dalbavancin: Phase 2/3 Integrated Database [Number (%) of Patients]

Preferred Term	Total Dalbavancin (n = 1778)	Total Comparator (n = 1224)
Patients with at least 1 AE	**799 (44.9)**	**573 (46.8)**
Nausea	98 (5.5)	78 (6.4)
Headache	83 (4.7)	59 (4.8)
Diarrhea	79 (4.4)	72 (5.9)
Constipation	52 (2.9)	30 (2.5)
Vomiting	50 (2.8)	37 (3.0)
Rash	38 (2.1)	22 (1.8)
Urinary tract infection	36 (2.0)	16 (1.3)

Abbreviations: AE = adverse event

8.4.3 Treatment-Related Adverse Events

Overall, the treatment-related AE profile in the phase 2/3 dalbavancin-treated patients was similar to, or better than, that in the comparator-treated patients, and the type and severity of treatment-related AEs were comparable for dalbavancin and comparators.

A smaller percentage of dalbavancin-treated patients reported treatment-related AEs than patients treated with a comparator drug. Treatment-related AEs were most commonly reported in the 'gastrointestinal disorders' SOC. Treatment-related AEs that occurred in ≥ 1% of patients in any treatment group are presented in Table 65.

Table 65 Treatment-Related Adverse Events Occurring in ≥ 1% of Patients in Either Treatment Group: Phase 2/3 Integrated Database [Number (%) of Patients]

Preferred Term	Total Dalbavancin (n = 1778)	Total Comparator (n = 1224)
Patients with at least 1 treatment-related AE	**328 (18.4)**	**246 (20.1)**
Nausea	49 (2.8)	40 (3.3)
Diarrhea	45 (2.5)	45 (3.7)
Headache	27 (1.5)	19 (1.6)
Gamma-glutamyltransferase increased	20 (1.1)	12 (1.0)
Rash	18 (1.0)	13 (1.1)
Vomiting	18 (1.0)	11 (0.9)
Pruritus	11 (0.6)	23 (1.9)

Comparators included linezolid 600 mg IV q12h (possible switch to 600 mg PO q12h); cefazolin 500 mg IV q8h (possible switch to cephalexin 500 mg PO q6h); vancomycin 1 g IV q12h (possible switch to an investigator selected oral agent); vancomycin 1 g q12h (possible switch to linezolid 600 mg PO q12h).
Abbreviations: AE = adverse event

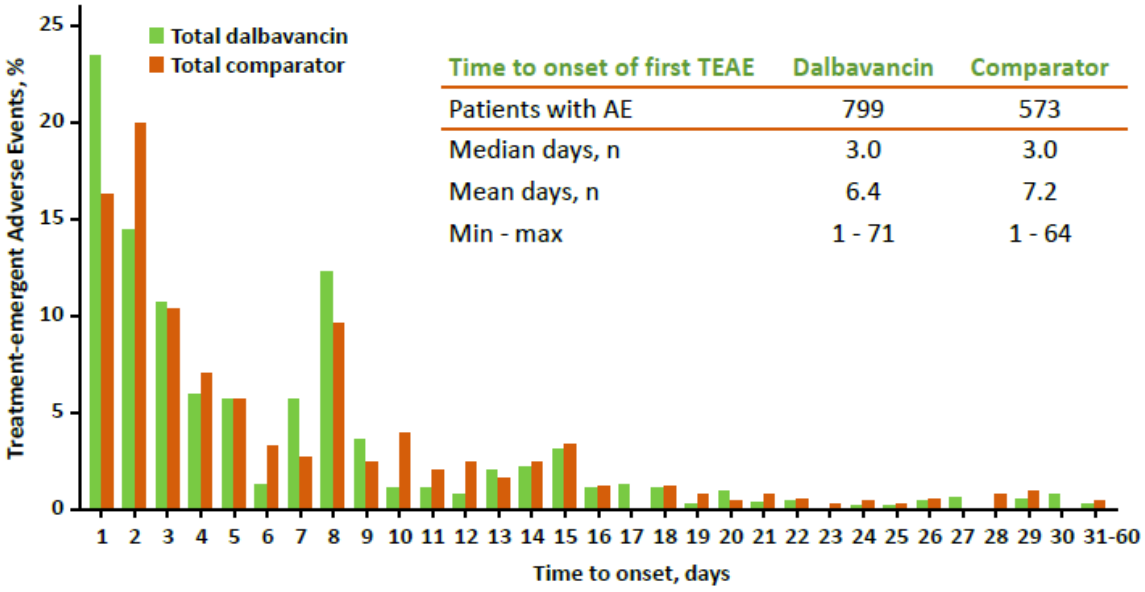
All other treatment-related AEs for both treatment groups were categorized as 'uncommon'(occurring at a frequency of ≥ 0.1% to < 1%).

8.4.4 Onset and Duration of Adverse Events

8.4.4.1 Day of Onset of Adverse Events

An overview of the time (day) of onset of adverse events is described in Figure 33. The onset of the majority of adverse events were reported in the early part of the study period. Late onset adverse events were seen at similar rates in patients treated with dalbavancin relative to those receiving comparator agents. The median (3.0 days each) and mean (6.4 vs. 7.2 days) day of onset of the first adverse event was similar for both dalbavancin and comparator treatment groups.

Figure 33. Day of Onset of Adverse Events: Phase 2/3 Integrated Safety Database



Time to onset of first TEAE	Dalbavancin	Comparator
Patients with AE	799	573
Median days, n	3.0	3.0
Mean days, n	6.4	7.2
Min - max	1 - 71	1 - 64

8.4.4.2 Duration of Adverse Events

Adverse events are summarized by duration of event in Table 66. Median TEAE duration for dalbavancin-treated versus comparator-treated patients was 3.0 and 4.0 days, respectively. Mean (SD) AE duration was similar between the two treatment groups: 7.7 (11.6) days for dalbavancin- treated patients and 8.0 (10.6) days for comparator-treated patients.

Table 66. Summary of Duration of Adverse Events – Overall

	Phase 2/3 Integrated Analysis Set		Phase 3 DUR001-301/302 Integrated Analysis Set	
	Dalbavancin (N=1778)	**Comparator (N=1224)**	**Dalbavancin (N=652)**	**Comparator (N=651)**
Number (%) subjects with at least 1 TEAE with available start/stop dates	799 (44.9)	573 (46.8)	214 (32.8)	247 (37.9)
AE duration (days)				
Number of events	1847	1335	462	517
Mean (SD)	7.7 (11.59)	8.0 (10.56)	8.7 (12.69)	8.7 (12.55)
Median	3.0	4.0	4.0	3.0
Min, Max	1, 197	1, 86	1, 101	1, 86
Number (%) subjects with ongoing AEs	252 (14.2)	192 (15.7)	40 (6.1)	59 (9.1)
Number of ongoing AEs	490	351	71	103
Number (%) subjects with AEs missing start/stop dates	33 (1.9)	28 (2.3)	3 (0.5)	8 (1.2)
Number of AEs missing start/stop dates	50	53	8	25

Duration is defined as event stop date - event start date + 1.Only adverse events with available start and stop dates are included in the computation of average duration. The average adverse event duration is summarized in the table.
Abbreviations: AE=adverse event, max=maximum, min=minimum, SD=standard deviation, TEAE=treatment emergent adverse event

For dalbavancin-treated patients in the overall phase 2/3 database, the median adverse event duration was 3.0 days (range: 1 to 197 days), versus a median duration of 4.0 days (range: 1 to 86 days) for comparator-treated patients.

The TEAEs with the longest duration for dalbavancin-treated subjects were as follows:

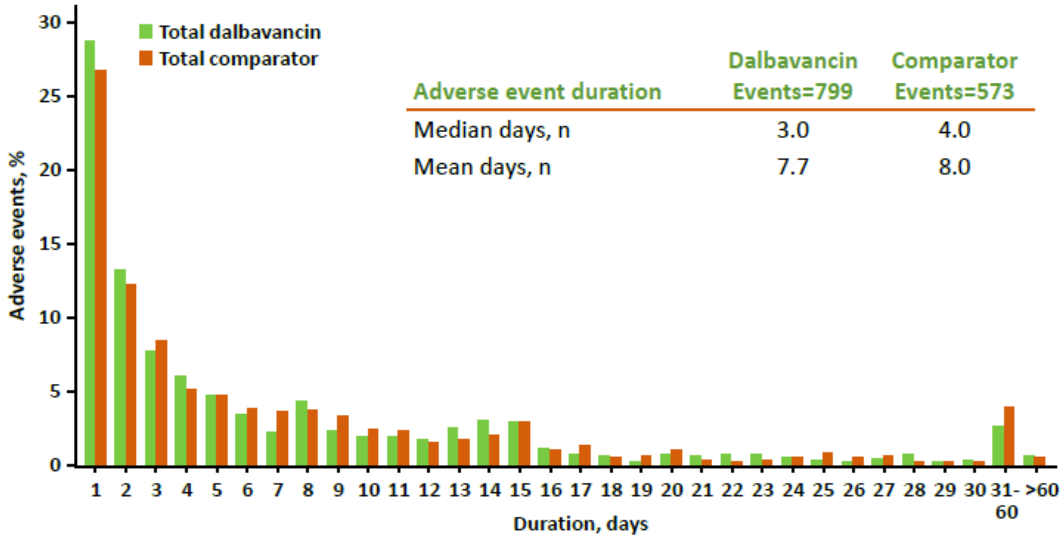
- Hypomagnesemia in a subject given 2 doses of dalbavancin that lasted for 197 days. The AE was considered by the investigator to be possibly related to study drug. This subject experienced no other AEs.
- Deep vein thrombosis in left lower extremity in a subject given 2 doses of dalbavancin that lasted for 102 days. The AE was considered by the investigator to be unrelated to study drug.
- Thrombocytosis in a subject given 2 doses of dalbavancin that lasted for 100 days, The AE was considered by the investigator to be possibly related to study drug.

- Worsening hypomagnesemia in a subject given 2 doses of dalbavancin that lasted for 98 days, The AE was considered by the investigator to be unlikely related to study drug. No cardiovascular or nervous system AEs were reported for this subject.
- Moderate dyspnea in a subject given 2 doses of dalbavancin that lasted for 100 days, severe arthritis bacterial that lasted for 96 days, and moderate constipation that lasted for 95 days. All events were considered by the investigator to be unrelated to study drug.

Of note, although 2 dalbavancin-treated subjects had AE reports of hypomagnesemia lasting > 95 days, no dalbavancin-treated subject had laboratory values for magnesium that met prospectively defined criteria for a PCS value.

In the total dalbavancin group, approximately 28.0% of TEAEs were a duration of 1 day, approximately 13.0% of TEAEs were a duration of 15 to 30 days, approximately 3.0% of the TEAEs were a duration of 31 to 60 days, and < 1.0% of the TEAEs were a duration of > 60 days; the remaining TEAEs varied from 2 days to 14 days in duration (Figure 34). The percentage of TEAEs with a specific duration (in days) was similar between dalbavancin-treated and comparator-treated patients.

Figure 34 Adverse Event Duration: Phase 2/3 Integrated Analysis Set



Adverse event duration	Dalbavancin Events=799	Comparator Events=573
Median days, n	3.0	4.0
Mean days, n	7.7	8.0

For comparator-treated subjects, the median TEAE duration was 4.0 days, with duration ranging from 1 to 86 days. The TEAE with the longest duration for comparator-treated subjects was blood alkaline phosphatase increased and gamma-glutamyltransferase increased which lasted for 86 days and was considered by the investigator to be probably related to study drug.

The AE profile and the duration of AEs in ABSSSI patients was similar to that in the overall phase 2/3 safety population.

8.4.5 Serious Averse Events and Deaths

The proportion of subjects experiencing SAEs was low and similar in the dalbavancin and comparator groups in the phase 2/3 (6.1% vs. 6.5%) and in the phase 1 (1.4% vs. 0) integrated analysis sets.

In the phase 2/3 studies, 109 (6.1%) dalbavancin-treated subjects and 80 (6.5%) comparator-treated subjects had at least 1 SAE. The most frequently occurring SAE was cellulitis, reported by 15 (0.8%) dalbavancin-treated subjects and 7 (0.6%) comparator-treated subjects. The incidence of subjects with cellulitis was similar between subjects who received 1 dose (or 7 days) of treatment and those who received 2 doses (or 14 days) of treatment.

Other than cellulitis, no SAE occurred with a frequency of ≥ 1% in any treatment group. A summary of SAEs occurring in 2 or more dalbavancin-treated subjects is presented by preferred term in decreasing frequency of the total dalbavancin group in Table 67.

Table 67. Serious Adverse Events by Decreasing Frequency in the Total Dalbavancin Arm (Occurring in ⩾ 2 Dalbavancin-Treated Subjects): Phase 2/3 Integrated Analysis Set

AE Preferred Term	Dalbavancin (N=1778)	Comparator (N=1224)
Number (%) of subjects with at least 1 SAE	109 (6.1)	80 (6.5)
Cellulitis	15 (0.8)	7 (0.6)
Cardiac failure congestive	4 (0.2)	2 (0.2)
Abscess limb	3 (0.2)	1 (0.1)
Asthma	3 (0.2)	0
Atrial fibrillation	3 (0.2)	1 (0.1)
Osteomyelitis	3 (0.2)	3 (0.2)
Anal abscess	2 (0.1)	1 (0.1)
Arthritis bacterial	2 (0.1)	0
Bacteraemia	2 (0.1)	1 (0.1)
Cardio-respiratory arrest	2 (0.1)	0
Cardiopulmonary failure	2 (0.1)	2 (0.2)
Deep vein thrombosis	2 (0.1)	2 (0.2)
Febrile neutropenia	2 (0.1)	0
Gastrointestinal haemorrhage	2 (0.1)	2 (0.2)
Impaired healing	2 (0.1)	1 (0.1)
Leukopenia	2 (0.1)	0
Myocardial infarction	2 (0.1)	0
Necrotising fasciitis	2 (0.1)	1 (0.1)
Peripheral ischaemia	2 (0.1)	0
Pneumonia	2 (0.1)	2 (0.2)
Pyrexia	2 (0.1)	1 (0.1)
Respiratory failure	2 (0.1)	0
Subcutaneous abscess	2 (0.1)	0

Note: Version 14.0 of MedDRA was used to code adverse events. Subject assignment to Dalbavancin 1 dose or Dalbavancin 2 doses is based on actual treatment and randomized treatment regimen for studies VER001-5, VER001-9, VER001-16 (for subjects with cSSSI). For Study VER001-4, all subjects are assigned to Dalbavancin 2 doses. For studies VER001-8 and VER001-16 (subjects with uSSSI), subject assignment to Dalbavancin 1 dose or Dalbavancin 2 doses is based on true exposure. For all studies, subject assignment to Comparator 7 days or Comparator 14 days is based on true exposure. Subjects are only counted once at each level of summarization. Adverse events are presented in decreasing frequency of preferred term for the total dalbavancin arm.
Abbreviations: AE= adverse event, SAE=serious adverse event

A total of 10 treatment-related SAEs were experienced in 3 (0.2%) subjects treated with dalbavancin and 9 (0.7%) subjects treated with comparator (Table 68). Except for acute renal failure (reported in 2 comparator-treated subjects), all treatment-related SAEs were reported in 1 subject. In addition, the Sponsor considered 1 case of leukopenia to be possibly related to treatment, even though the investigator did not.

One of these serious adverse drug reactions required expedited reporting: a subject in ABSSSI study DUR001-302 with anaphylactoid reaction whose symptoms resolved quickly with standard treatment and did not recur.

The subject was a 22-year-old White male with a past medical history of reactive airway disease, treated with 1 dose of IV dalbavancin, developed severe, life-threatening "anaphylactic and reactive bronchospasm", consisting of dyspnea, laryngospasm, and hypotension/shock. The onset of this event, which was assessed as possibly related to study medication by both the investigator and the sponsor, was approximately 15 minutes after the start of the planned 30-minute IV infusion of dalbavancin 1000 mg on Day 1 of study treatment. The subject had also received general anesthetic agents approximately 3 hours prior and IV aztreonam immediately prior to the start of the dalbavancin infusion. The dalbavancin infusion was stopped in response to the event, and the subject was treated immediately with epinephrine, hydrocortisone, midazolam, famotidine, chloropyramine, and clemastine. Endotracheal intubation was not required, and the symptoms and signs associated with the event were considered to be completely resolved within approximately 1 hour of initiation of treatment with dalbavancin.

Table 68. Treatment-Related Serious Adverse Events: Safety Population

Treatment-related Serious Adverse Event(s)	Body System	Related to Study Drug
Phase 1 Integrated Analysis Set, Dalbavancin group		
None reported	NA	NA
Phase 2/3 Integrated Analysis Set, Dalbavancin group		
Leukopenia	Blood and lymphatic system disorders	Probably related
Cellulitis	Infections and infestations	Possibly related
Anaphylactoid reaction	Immune system disorders	Possibly related
Phase 2/3 Integrated Analysis Set, Comparator group		
Renal failure acute	Renal and urinary disorders	Probably related
Pancreatitis acute	Gastrointestinal disorders	Possibly related
Thrombocytopenia	Blood and lymphatic system disorders	Probably related
Pancytopenia	Blood and lymphatic system disorders	Possibly related
Face oedema	General disorders and administration site conditions	Probably related
Cellulitis	Infections and infestations	Probably related
Nephropathy toxic	Renal and urinary disorders	Possibly related
Gastrointestinal disorder	Gastrointestinal disorders	Possibly related
Renal failure acute	Renal and urinary disorders	Probably related

The incidence of patients with TEAEs with the outcome of death was similar between the dalbavancin and comparator groups in the phase 2/3 integrated analysis set (10 [0.6%] vs. 14 [1.1%] patients). All AEs that resulted in death were considered by the investigator to be unrelated or unlikely related to study treatment; all deaths were considered by the investigator to be unrelated to study drug. The percentages of patients who died in each treatment group were similar. There was no single common etiology causing death. All deaths that occurred during the dalbavancin phase 2/3 clinical program are tabulated in Table 69. No subject died during the dalbavancin phase 1 clinical development program.

Table 69. Number of Deaths that Occurred during the Dalbavancin Clinical Program

Number of deaths due to:	Phase 1 Integrated Analysis Set		Phase 2/3 Integrated Analysis Set		Phase 3 DUR001-301/302 Integrated Analysis Set	
	Dalbavancin (N=286)	Comparator (N=122)	Dalbavancin (N=1778)	Comparator (N=1224)	Dalbavancin (N=652)	Comparator (N=651)
Any AE[a]	0	0	10	15	1	8
TEAE[b]	0	0	10	14	1	7
TEAE during study period	0	0	10	13	1	7

[a] Any AE refers to events occurring during before, during, or after the study period; 1 death occurred after the last TOC visit and is included in te total.
[b] 1 death was due to a non-treatment-emergent AE and is not included in this total.

Abbreviations: AE= adverse event, TEAE= treatment-emergent adverse event

8.4.6 Adverse Events of Special Interest

8.4.6.1 Hepatic Adverse Events and Liver Function Abnormalities

Hepatic adverse events and adverse events related to liver function were extensively monitored during the dalbavancin clinical program based on the results from nonclinical studies (Sections 4.3.4.1 and 8.4.1). No signal of abnormal hepatobiliary function was observed in subjects treated with dalbavancin relative to those treated with the comparator regimen in the phase 2/3 integrated analysis set. The incidences of subjects with hepatobiliary disorder AEs were low and similar between the dalbavancin and comparator treatment groups (1.0% vs. 0.7%) and few events were considered by the investigator to be related to study drug (0.3% vs. 0.1%). Serious adverse events (SAEs) of hepatobiliary disorders were uncommon in both the dalbavancin and comparator groups (0.2% in each group) and all were assessed as unrelated to study drug by the investigator.

A slightly higher proportion of subjects in the dalbavancin group was noted to have elevated serum transaminases on treatment relative to patients treated with comparator agents (ALT $\geq$ 3x ULN and 3-fold increase from baseline: 0.5% in the dalbavancin group vs 0.1% in the comparator group; AST $\geq$ 3x ULN and 3-fold increase from baseline: 0.6% in the dalbavancin group vs 0.1% in the comparator group; Table 70). However, at the end of therapy, the incidences of liver function abnormalities was similar between treatment groups (ALT $\geq$ 3x ULN and 3-fold increase: 0.4% in the dalbavancin group vs 0.3% in the comparator group; AST $\geq$ 3x ULN and 3-fold increase: 0.2% in the dalbavancin group compared with 0.3% in the comparator group).

Table 70. Hepatobiliary Laboratory Values, Phase 2/3 Integrated Safety Database

Clinical laboratory parameter (potentially clinical significant criteria)	Patients, n (%)			
	On Treatment		End of Treatment	
	Dalbavancin	Comparator	Dalbavancin	Comparator
ALT (≥ 3×ULN and ≥ 3-fold ↑)	6 (0.5)	1 (0.1)	6 (0.4)	3 (0.3)
AST ((≥ 3×ULN and ≥ 3-fold ↑)	8 (0.6)	1 (0.1)	3 (0.2)	3 (0.3)
Alk phos (≥ 1.5×ULN and ≥ 2-fold ↑)	8 (0.6)	4 (0.4)	9 (0.6)	6 (0.6)
Tot. bilirubin (≥ 1.5×ULN and ≥ 3-fold ↑)	1 (0.1)	0	2 (0.1)	1 (0.1)

Abbreviations: Alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

A shift analysis that evaluates evolution of serum aminotransferases from baseline also revealed similar proportions of patients developing post-baseline elevations in serum aminotransferases within each treatment group as shown in Table 71.

Table 71. Shift Analyses Table: ALT, AST; Phase 2/3 Safety Population

		On-treatment			EOT		
			Patients, n (%)			Patients, n (%)	
Parameter	Baseline	N (a)	Normal	High	N (a)	Normal	High
Dalbavancin							
ALT	Normal	1083	970 (89.6)	113 (10.4)	1258	1142 (90.8)	116 (9.2)
	High	178	54 (30.3)	124 (69.7)	206	83 (40.3)	123 (59.7)
AST	Normal	1076	968 (90.0)	108 (10.0)	1256	1154 (91.9)	102 (8.1)
	High	162	64 (39.5)	98 (60.5)	191	98 (51.3)	94 (49.2)
Comparator							
ALT	Normal	765	695 (90.8)	70 (9.2)	842	760 (90.3)	82 (9.7)
	High	167	48 (28.7)	119 (71.3)	176	69 (39.2)	107 (60.8)
AST	Normal	746	679 (91.0)	67 (9.0)	838	782 (93.3)	56 (6.7)
	High	160	66 (41.3)	94 (58.8)	166	92 (55.4)	74 (44.6)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; EOT = end of therapy

The majority of subjects with normal ALT values at Baseline who subsequently developed abnormal ALT values on or after treatment had ALT elevations that were < 10 times ULN (Table 72).

Table 72. Elevated ALT in Patients with Normal ALT Values (< 45 U/L) at Baseline; Phase 2/3—Safety Population

	Patients, n/N1 (%)	
Highest ALT values at visit	**Dalbavancin**	**Comparator**
ALT ≥ 3× to 5×ULN		
Day 3	4/1083 (0.4)	0/765
EOT	2/1258 (0.2)	1/842 (0.1)
TOC	1/778 (0.1)	0/363
ALT ≥ 5× to 10×ULN		
Day 3	1/1083 (0.1)	0/765
EOT	0/1258	1/842 (0.1)
TOC	1/778 (0.1)	0/363
ALT ≥ 10×ULN		
Day 3	0/1083	0/765
EOT	2/1258 (0.2)	0/842
TOC	1/778 (0.1)	0/363

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

There were 2 subjects in the dalbavancin group who had normal ALT values at baseline and developed ALT values ≥ 10× ULN at EOT. Both subjects had other reasons that caused or contributed to the ALT elevations; ongoing alcohol use and injection of IV heroin on the day of the EOT visit in the setting of hepatitis C in one case and gallstone related cholestasis in the other. In both cases, serum ALT levels returned to normal by Day 20. There was one subject who had a normal ALT value at baseline and subsequently developed ALT value ≥10× ULN at the TOC visit. This subject reportedly was on vacation from Day 23 to Day 25 and had been drinking an excess of alcohol during that time just prior to the TOC visit. Folow-up values obtained on Day 35 revealed improving ALT values and laboratory values on Day 357 were entirely normal.

There was no evidence of altered liver function accompanying or promptly following elevation of aminotransferases, such as an increase in serum total bilirubin unexplained by other causes. There were no cases of Hy's law (Temple 2001, Reuben 2004) seen in the dalbavancin clinical program. Furthermore, the proportion of cases with aminotransferase elevations to ≥ 3× upper limit of normal in the dalbavancin group was comparable to that seen in the comparator group. Therefore, based on the FDA guidance for Industry (*Drug Induced Liver Injury: Premarketing Clinical Evaluation*, July 2009), dalbavancin has a low potential for causing severe drug induced liver injury.

8.4.6.2 Renal Adverse Events and Renal Function Laboratory Test Abnormalities

The kidney was identified as a target organ in nonclinical studies (Section 4.3.4.1), and renal effects were carefully monitored in the clinical program. In the phase 2/3 integrated analysis set, the frequency of AEs in the renal disorder SOC was similar in the dalbavancin and

comparator groups (1.9% vs. 2.0%). Treatment-related renal disorder AEs (0.2% vs. 0.4%) and serious renal disorder AEs (0.2% vs. 0.5%) were similar in the dalbavancin and comparator groups, respectively.

Systematic review of renal laboratory test parameters, including BUN and serum creatinine, did not suggest nephrotoxicity in patients treated with dalbavancin.

8.4.6.3 Hematologic Laboratory Test Results

Some antibiotics, such as linezolid (Gerson 2002) and vancomycin (Rao 2004), have been associated with myelosuppressive effects on haematological parameters. Adverse events potentially related to myelosuppression were therefore examined and are summarized below.

In the phase 2/3 integrated analysis set, the frequencies of individual myelosuppression AEs were similar in the dalbavancin (0.1-1.9%) and comparator (0.1-1.6%); treatment-related myelosuppression AEs and SAEs were similar in the two groups. In the phase 1 integrated analysis set, anaemia, thrombocytopenia, and platelet count decreased were each reported in 1 (0.4%) subject exposed to dalbavancin and no subject exposed to comparator (mostly placebo) in the phase 1 integrated analysis set.

The frequency of treatment-related myelosuppression AEs was similar between subjects treated with dalbavancin (0.1-0.3%) and subjects treated with a comparator (0.1-0.7%). The AEs considered possibly or probably related to treatment with dalbavancin (or the relationship was missing) in 0.1 to 0.3% of subjects included: anaemia, leukopenia, neutropenia, thrombocytopenia, haemoglobin decreased, and platelet count decreased. The AEs considered possibly or probably related to treatment with a comparator (or the relationship was missing) in 0.1 to 0.7% of subjects included: thrombocytopenia, leukopenia, neutropenia, pancytopenia, platelet count decreased, monocyte count decreased, and red blood cell count decreased.

In the comparator group, 7 of 9 cases of thrombocytopenia were considered to be possibly or probably related to treatment. By comparison, 1 of 7 cases of thrombocytopenia in the dalbavancin group was considered to be related to treatment. This finding is not unexpected, as 7 of the 9 comparator-treated subjects with thrombocytopenia had received linezolid, which has been associated with some myelosuppressive effects, particularly thrombocytopenia (Weigelt 2005). There were otherwise no clear differences between the two treatment groups with respect to treatment related AEs potentially indicating myelosuppression.

A review of the laboratory parameters for platelets also revealed a numerically lower proportion of dalbavancin-treated subjects who were noted to have thrombocytopenia at EOT relative to comparators (Table 73). This was most pronounced in study VER001-9, where linezolid was used as the sole comparator (0.7% of subjects in the dalbavancin group and 6.3% of subjects in the linezolid arm had at least a 40% decrease in platelets at EOT).

Table 73. Platelet parameters at EOT from Study VER001-9 and Phase 2/3 Integrated Database

Analysis Population	40% decrease in platelet counts from baseline n/N (%)	Shift from normal platelet counts at baseline to <LLN n/N (%)	≤0.6 x LLN and ≥0.4-fold decrease in platelet counts n/N (%)
Study VER001-9			
Dalbavancin	3/451 (0.7)	6/384 (1.6)	0/451 (0.0)
Linezolid	14/ 236 (5.9)	17/205 (8.3)	2/236 (0.9)
Phase 2/3 Integrated Safety Database			
Dalbavancin	8/1467 (0.5)	19/1213 (1.6)	2/1467 (0.1)
Comparators	22/1018 (2.2)	35/845 (4.1)	4/1018 (0.4)

The frequency of serious myelosuppression AEs was similar between subjects treated with dalbavancin (0.1%) and subjects treated with a comparator (0.1%). SAEs related to myelosuppression included sickle cell anaemia with crisis, febrile neutropenia, leukopenia, and anaemia, each of which were reported in 0.1% of subjects treated with dalbavancin; only leukopenia was considered by the investigator to be possibly or probably related to treatment in 1 subject who was a 47 year old man with normal hematology parameters at baseline, treated with two doses of dalbavancin and noted to have a WBC count of 4.0 x $10^3/\mu L$ on day 9, $3.7x10^3/\mu L$ on Day 15 and within normal limits ($7.7x10^3/\mu L$) on Day 29. SAEs related to myelosuppression included pancytopenia and thrombocytopenia, each of which were reported in 0.1% of subjects treated with a comparator; both of these SAEs were considered possibly or probably related to treatment. None of the AEs related to myelosuppression had an outcome of death.

Of the phase 2/3 patients, ≤ 3% of dalbavancin or comparator-treated patients had low potentially clinically significant values (PCS) or potentially clinically significant changes (PCSC) for WBCs during the study, and these values were generally mild and transient. Most patients with low PCS values had the relevant hematology abnormalities present at Baseline. The percentage of patients who had treatment-emergent, clinically significantly abnormal hematology values was low and similar between dalbavancin and comparator treated patients.

Overall, the safety profile of dalbavancin with respect to AEs potentially related to myelosuppression was better than that of comparator treatments, particularly linezolid.

8.4.6.4 Infusion Site-Associated and Systemic Infusion-related Adverse Events

In the phase 2/3 integrated analysis set, the dalbavancin and comparator groups had similar frequencies of infusion site-associated AEs (2.2% vs. 3.1%), treatment-related infusion site-associated AEs, and serious infusion site-associated AEs (none in either group). In the phase 1 integrated analysis set, few infusion site-associated AEs were reported.

The frequencies of treatment-related infusion site-associated AEs were also comparable between the 2 treatment groups. Infusion site-associated AEs considered possibly or probably related to treatment with dalbavancin (or the relationship was missing) in 0.1 to 0.6% of subjects included: infusion site coldness, erythema, extravasation, inflammation, irritation, edema, pain, phlebitis, rash, reaction, and swelling; infusion-related reaction; injection site discomfort, irritation, pain and pruritus. Infusion site-associated AEs considered possibly or probably related to treatment with a comparator (or the relationship was missing) in 0.1 to 0.7% of subjects included: infusion site pain, erythaema, extravasation, swelling, reaction, oedema, inflammation, and irritation; infusion related reaction, and pruritus. The majority of infusion related AEs associated with dalbavancin did not occur on the days when dalbavancin was infused and were related to the presence of an indwelling catheter. No infusion site-associated SAEs or deaths were reported.

There was no clear pattern of systemic infusion-associated reactions in either treatment group. There were no cases of Red-Man syndrome or anaphylaxis in any dalbavancin-treated patient. However, 2 vancomycin-treated patients reported Red-Man syndrome.

8.4.6.5 Potential Adverse Events Related to Effects on Glucose Homeostasis

Dysglycemias may be correlated with poor outcome in post-surgical patients, particularly those undergoing cardiac surgery (Murray et al, 2004). With respect to antibiotics, effects on glucose homeostasis are most closely associated with fluoroquinolones, such as gatifloxacin, and have resulted in several label changes for that compound (Park-Wyllie 2006). No preclinical data suggesting an effect on pancreatic endocrine (beta cell) function had been observed with dalbavancin. Nevertheless, AEs potentially related to glucose homeostasis are summarized below.

The incidences of subjects with AEs potentially related to effects on glucose homeostasis were low and similar between the dalbavancin and comparator treatment groups. Few of these events were considered by the investigator to be related to study drug. Serious adverse events potentially related to effects on glucose homeostasis were uncommon in the dalbavancin and comparator groups (0.1% in each group) and all were assessed as unrelated to study drug. The frequencies of glucose-related laboratory abnormalities (both hyperglycemia and hypoglycemia) were similar in dalbavancin- and comparator-treated subjects. Additionally, confounding factors likely to contribute to the development of dysglycemia were present in the majority of the clinical cases of laboratory hypoglycemia or hyperglycemia. Based on these data and non-clinical data, where no pancreatic beta-cell morphologic effects of any kind were observed at any dose level in the toxicology studies of dalbavancin in rats and dogs, and where no treatment-related pancreatic changes of any kind were observed in dalbavancin-treated dogs, there is no evidence to suggest a treatment-related effect of dalbavancin on glucose homeostasis.

8.4.6.6 Potential for Gastrointestinal Adverse Events

Diarrhea is a frequently reported AE in trials of antibiotics, and *Clostridium difficile* (a Gram-positive anaerobic bacterium) is a major causative agent of colitis and diarrhea following antibiotic usage.

In the phase 2/3 studies, diarrhea was reported by 79 (4.4%) dalbavancin-treated patients and 72 (5.9%) comparator-treated patients. Of these events, diarrhea was reported by 35 (5.6%) dalbavancin-treated cSSSI patients and by 32 (9.9%) comparator-treated cSSSI patients. Another preferred term consistent with *C. difficile* diarrhea, *C. difficile* colitis, was reported in 4 (0.2%) of dalbavancin-treated subjects and 1 (0.1%) comparator-treated subject. All of these TEAEs, except for 1 case of severe *C. difficile* colitis in the dalbavancin group unrelated to study drug, were moderate and considered to be possibly related to study drug. Other information relevant to the *C. difficile* AE in patients treated with dalbavancin include: one patient who had been on piperacillin/tazobactam prior to randomization; one patient had been receiving metronidazole for empiric treatment of diarrhea prior to admission; and the *C. difficile* colitis in another patient was associated with severe constipation alternating with diarrhea, although the diarrhea was intermittent, mild, and considered unrelated to study drug.

As *C. difficile* colitis must be considered in all patients who present with diarrhea following antibiotic use, an appropriate warning will be included in the proposed product labeling. This is consistent with the approach currently undertaken for other antibacterial medications. Routine pharmacovigilance, as dictated by antibacterial class labeling, is generally employed to assess the occurrence of *C. difficile* colitis.

8.4.6.7 Adverse Events in Pediatric Patients

The tolerability of a single dose of 1000 mg or 15 mg/kg IV dalbavancin, administered in addition to background anti-infective treatment, were investigated in 10 adolescent subjects aged from 12 to 16 years, that were hospitalized for a known or suspected bacterial infection (Study A8841004). Five subjects in the dalbavancin 1000 mg group and 4 subjects in the 15 mg/kg group experienced AEs. There were no treatment-related AEs and no severe AEs. There was 1 SAE, mild ileus, experienced by 1 subject in the 15 mg/kg group. This SAE was considered by the investigator to be related to complications following an intra-abdominal abscess and not related to treatment. There were no temporary or permanent discontinuations or dose reductions of treatment due to AEs. Headache, experienced by 1 subject in each group, was the only AE to be experienced by more than 1 subject. AEs experienced in the 1000 mg group were diarrhea, nausea, vomiting, increased blood bilirubin, headache, nasal congestion and hypotension. AEs experienced in the 15 mg/kg group were abdominal pain, constipation, ileus, hyperbilirubinemia, skin laceration, wound, dehydration, dizziness, headache and rash macular. The only AE of moderate severity was headache in the 1000 mg group; all other AEs were of mild severity.

Four subjects in the 1000 mg group and 4 subjects in the 15 mg/kg group were reported to have laboratory test abnormalities without regard for Baseline value. Increased blood bilirubin (1 subject in the 1000 mg group, causality: possibly related to alcohol use) and hyperbilirubinemia (1 subject in the 15 mg/kg group, causality: disease under study) were recorded as AEs and therefore clinically significant. None of the changes from Baseline in vital sign and ECG measurements were considered to be clinically significant.

The safety profile of dalbavancin in the subjects aged between 12 and 16 years in this study was acceptable and consistent with observations reported in the adult studies.

8.4.7 Potential for Drug-Drug Interactions

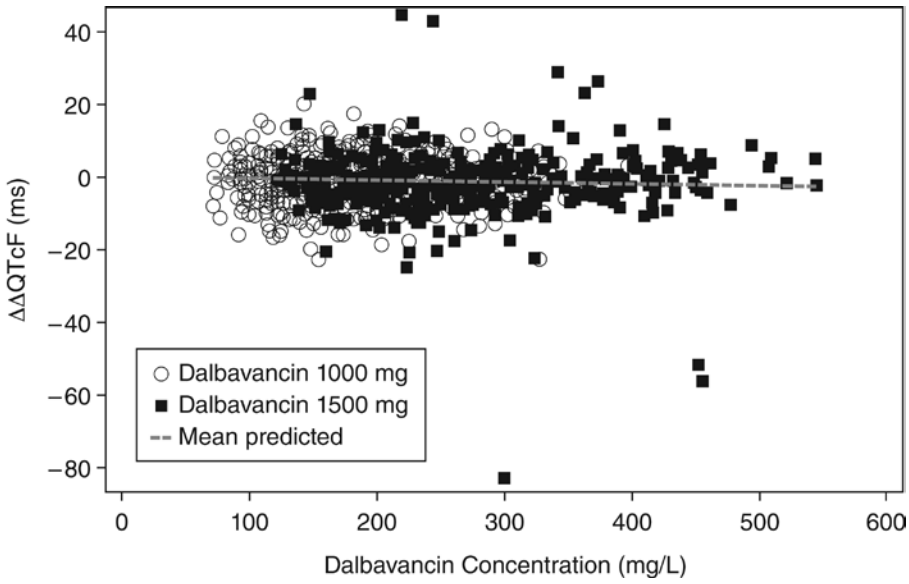
No specific drug-drug interactions have been observed in dalbavancin-treated subjects. Dalbavancin displayed little or no significant affinity for any receptor, ion channel, uptake site, or enzyme tested at a concentration of 100 μM, which approximates peak plasma levels at therapeutic doses (Section 4.1.2.3). Where binding or enzyme inhibition values were observed in some systems, these had low margins compared to C_{max}. Taken together with the plasma concentration decrease by approximately 75% by 48 hours after injection, and the results of nonclinical toxicology studies and clinical AE reports, it is not expected that the results of the in vitro assays translate to biologically significant effects in animals or subjects. In addition, these results do not indicate a likely interaction with other therapeutic targets or a potential for clinically relevant PD interactions.

8.5 Special Safety Investigations

8.5.1 Cardiac Safety

The impact of dalbavancin as single-dose IV infusion of 1000 mg and 1500 mg on the 12-lead ECG QTcF interval was examined in a phase 1 Thorough QT study in 200 adult healthy male and female volunteers (Study DUR001-102). In this study, dalbavancin did not have an effect on the QTcF interval and an effect exceeding 10 msec could be confidently excluded at all time points after a single IV dose of 1000 mg and after a single IV dose of 1500 mg. There were no time points at which QTcF exceeded 480 msec or 500 msec in any of the treatment groups and a change-from-Baseline QTcF exceeding 30 msec was observed in only 1 subject in the dalbavancin groups (1500 mg). Occasional T-wave morphology changes were observed. Most of these occurred in the placebo and moxifloxacin groups. Dalbavancin did not exert a relevant effect on the heart rate or on the PR or QRS intervals. Assay sensitivity was demonstrated by the expected ΔΔQTcF effect of 400 mg moxifloxacin, which peaked at 2 hours (mean 12.9 msec). The lower bound of the 90% CI exceeded 5 msec at all 3 pre-identified time points. The relationship between the individually observed dalbavancin concentrations and associated ΔΔQTcF is shown in Figure 35.

Figure 35 Observed ΔΔQTcF Versus Dalbavancin Plasma Concentration Data With Population Mean Predictions Overlaid



The predicted ΔΔQTcF at the geometric mean peak dalbavancin plasma concentration observed after 1000 mg (285 µg/mL; CI: 275 to 294) was -1.5 msec and after 1500 mg (421 µg/mL, CI: 408 to 434) was -2.1 msec. These results are consistent with the time matched analysis and confidently demonstrate that dalbavancin does not affect the QTc interval in a clinically relevant way.

During the phase 2/3 clinical development program, ECGs from a substantial number of patients were examined. Paired ECG data were available for 382 dalbavancin-treated patients and 199 comparator-treated patients and were analyzed in a blinded fashion by a centralized reviewer. Dalbavancin had no effect on the QT interval and no clinically significant ECG results reported in dalbavancin treated patients. The ECG results of the phase 2/3 integrated analysis set demonstrate that dalbavancin does not exhibit any impact on heart rate, atrio-ventricular conduction, intra-ventricular conduction, or repolarization.

8.5.2 Potential for Ototoxicity

Audiometric testing was undertaken in the phase 1 study, VER001-1 as ototoxicity has been identified as an AE during treatment with glycopeptides antibiotics such as vancomycin. In this study, abnormal audiograms were recorded for 5 subjects treated with dalbavancin and 2 treated with placebo. Audiometric testing was therefore undertaken in other phase 1 studies conducted during the development program.

In the dalbavancin development program, a total of 105 phase 1 subjects dosed with dalbavancin have undergone stringent audiologic testing. All audiology data have been reviewed by a single central reviewer. Careful review of the totality of the data did not suggest any evidence of ototoxic change associated with dalbavancin. An expert assessment of audiology findings for the 6 phase 1 studies in which audiology assessments were

conducted found no results that were suggestive of any pattern of ototoxic change associated with dalbavancin.

8.5.3 Potential for Effects on Vital Signs

Vital sign measurements included pulse, respiration rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP), and oral body temperature. Sponsor-defined criteria were used to identify PCS values or PCSC in results (Table 74).

Table 74 Criteria for Identifying PCS and PCSC Vital Sign Results

Parameter (units)	Normal Range	PCS Low Value	PCS High Value	PCSC Decrease in Value	PCSC Increase in Value
Pulse (bpm)	60-100	< 50	> 120	0.5×	2×
Respiration rate (bpm)	---	< 8	> 32	---	---
Systolic blood pressure (mmHg)	95-145	< 85	> 200	0.2×	1.6×
Diastolic blood pressure (mmHg)	60-95	< 50	> 120	0.2×	1.2×
Oral temperature (°Celsius)	---	---	---	2°	2°

Note: The change from Baseline was tabulated as a PCSC only if the post-Baseline value for the parameter was outside of the defined normal ranges.
Abbreviations: PCS= potentially clinically significant; PCSC= potentially clinically significant change

In the phase 1 integrated analysis set, where necessary to harmonize assessment times post-dose for trials where data collection of vital signs was different, data conventions were adopted regarding utilization of common assessment times as close as possible to the defined time points (ie, 4 and 12 hours post-dose). Similar assessment times harmonization conventions were utilized across phase 2/3 trials in which data collection times were different. Separate analyses were utilized when trial protocols required administration of 1 dose or 2 doses of dalbavancin (equivalent to 7 days or 14 of daily comparator, respectively). Vital sign data in phase 2/3 trials were also summarized by baseline liver or renal impairment criteria. Respiration was not summarized as a PCSC in the phase 2/3 integrated analysis set.

Overall, in the phase 1 integrated analysis set, there were few PCS values or changes from Baseline in vital sign parameters, with the exception of DBP increase. In the integrated 2 and phase 3 DUR001-301/302 databases, there were few (generally <5% of subjects) PCSC from Baseline in vital sign parameters of blood pressure, pulse, or increases in oral temperature in the integrated phase 1and phase 3 databases, indicating that dalbavancin has no observable effect on these vital sign parameters above that of the comparators studied. In the integrated phase 2 and phase 3 DUR001-301/302 databases, decreases in oral temperature that met the PCSC criteria were more common (up to 25% of subjects), reflecting results of treatment. No trends in PCSC in vital sign results were observed by Baseline creatinine level or Baseline hepatobiliary status. Results were similar between dalbavancin and comparator treatment groups. Results in the phase 3 DUR001-301/302 database were similar to those in the phase 2/3 integrated analysis set.

8.5.4 Potential for Lack of Effectiveness Associated with Emergence of Resistance

Susceptibility of clinical isolates from worldwide surveillance studies and phase 2/3 clinical trials are summarized in Section 7.

Resistance to glycopeptides is rare in targeted Gram-positive organisms responsible for SSSI (principally *S. aureus* and *Streptococcus* spp.). High-level glycopeptide resistance, affecting both vancomycin and teicoplanin, requires the presence of the VanA cluster. VanA consists of several genes needed to substitute the altered cell wall precursor peptide D-ala-D-lac for the normal D-ala-D-ala, as well as regulatory genes that respond to both glycopeptides. Multi-genic resistance of this type cannot simply be selected by exposure to glycopeptides, but requires the presence of another organism that already possesses these determinants and can transfer them. The development of resistance (ie, stably increased MIC) in bacteria exposed to dalbavancin in vitro or in animal infection studies has not been observed. Dalbavancin resistance did not arise in serial passage experiments conducted in 2 different laboratories, with a total of 8 staphylococcal isolates, including MRSA, VISA and methicillin-resistant coagulase-negative staphylococci (Lopez 2005; Goldstein 2007). Importantly, no increase in dalbavancin MIC was seen with the VISA strain. In an attempt to select single-step resistant variants, direct selection experiments were conducted in 2 different laboratories with a total of 6 *S. aureus* (including MRSA and VISA) and 1 MRSE. In these studies, dalbavancin demonstrated a low potential for selecting spontaneously resistant mutants and no single-step high-level resistance was observed. Additionally:

- Among more than 11,000 isolates of *Staphylococcus* spp. tested, there was only a single vancomycin-resistant *S. aureus* (Michigan) strain with reproducible resistance to dalbavancin.
- The maintenance of bactericidal levels of dalbavancin throughout the treatment period with the proposed dalbavancin doses in humans may be expected to reduce the potential for resistance emergence in vivo.

While it is difficult to offer definitive predictions about the development of resistance to dalbavancin, the results of the above-mentioned studies as well as dalbavancin's sustained concentrations above the MIC for Gram-positive skin pathogens throughout the dosing interval, suggest a low potential for resistance development.

8.6 Overdose, Potential for Dependence, Rebound or Abuse

Dose-limiting toxicity with dalbavancin has not been observed. Three treatment groups of 3 healthy adult subjects each received total dalbavancin exposures of 4500 mg (3.0-fold the proposed therapeutic exposure), 3500 mg (2.3-fold the proposed therapeutic exposure), and 2500 mg (1.7-fold the proposed therapeutic exposure) in a planned multiple dose phase 1 clinical trial. An additional 58 subjects received single doses of 1500 mg dalbavancin, or 150% of the recommended initial dalbavancin therapeutic dose. Overall, single doses and multiple doses of dalbavancin exceeding the recommended therapeutic doses were well-tolerated when administered to healthy subjects. A single 3000 mg dalbavancin infusion was

accidentally initiated for a patient in a phase 3 trial, and upon the discovery of the dosing error, the infusion was stopped. The subject received approximately 1530 mg of dalbavancin over a 15-minute infusion and did not experience any TEAEs.

Treatment of overdose with dalbavancin should consist of observation and general supportive measures. Although dalbavancin is not measurable in dialysate, concentration-time profiles for subjects with ESRD have been shown to be more similar to subjects with normal renal than for the severe renal impairment group. This indicates that dalbavancin concentrations are impacted by hemodialysis.

Considerations regarding dependence, rebound, and abuse are not relevant to dalbavancin.

8.7 Safety Conclusions

The safety and tolerability profile of dalbavancin was consistent across studies and populations (demographic subgroups, special populations). The safety and tolerability profiles for the dalbavancin treated patients were comparable to that seen for those treated with the comparator agents. The types of AEs identified are those typically seen in patients enrolled in clinical trials of SSSI and can be managed by discontinuation of study drug therapy or with standard medical therapies. Most AEs were of mild intensity and resolved spontaneously.

9 OVERALL ASSESSMENT OF BENEFIT-RISK

9.1 Medical Need

Skin and skin structure infections (SSSI) are among the most common infections in the US and throughout the world, and remain a significant source of morbidity and mortality in the nosocomial and community settings, despite improved understanding of risk factors and an array of antibiotics and prophylactic measures that can be instituted (Wilson 2003; Spellberg 2009). These infections can range in severity from uncomplicated skin and skin structure infections (uSSSI), such as simple folliculitis, to complicated skin and skin structure infections (cSSSIs), such as necrotizing fasciitis and Fournier's gangrene. Acute bacterial skin and skin structure infections involve deeper soft tissue than uncomplicated infections, and may require significant surgical intervention and parenteral antibiotic therapy (Fung 2003).

The risk factors which predispose patients to cSSSIs/uSSSIs include the following (Source: DiNubile 2004; Itani 2005; Turina 2005; Groom 2001, Castrodale 2004):

- Local factors: soft tissue trauma (both blunt and sharp), animal or human bite injuries, burn injuries, operative wounds, contaminated wounds, peripheral vascular disease, obesity, poor hygiene, presence of a foreign body (ie, piercings), venous insufficiency and stasis;
- Systemic factors: diabetes mellitus (especially if poorly controlled), acute hyperglycaemic episodes in patients with or without diabetes, malnutrition, immunocompromised states (human immunodeficiency virus, cellular or humoral immune deficiencies), drugs (corticosteroids, cyclosporine, chemotherapy, etc.), sensory neuropathies, chronic systemic illness, elderly, ethnicity, colonization.

Within the hospital or long-term care setting, cSSSIs/ABSSSIs are generally a consequence of surgery or regarded as a secondary infection associated with an underlying disease. Surgical site infections are the third most frequently reported nosocomial infections, accounting for 17% of all nosocomial infections among hospitalized patients (Centers for Disease Control and Prevention, 1999). Patients who have other infections at a remote body site, are colonized with other microorganisms, are on steroids, have undergone chemotherapy, or have a prolonged length of hospital stay or previous hospitalization are more prone to serious SSSI (Itani, 2005). Within the community, cSSSIs/ABSSSIs are often associated with the consequences of trauma. Patients who are elderly, have poor nutritional status, have diabetes, smoke, or are obese are at risk of severe forms of SSSI (DiNubile 2004; Itani 2005; Turina 2005).

While the exact incidence of SSSIs is unknown, it has been reported that an increase in the incidence of SSSI overall has been observed as a result of a number of risk factors such as aging of the general population, an increase in the number of critically ill patients, a higher incidence of immunocompromised patients (eg, those with HIV infection, cancer patients receiving chemotherapy, organ transplant recipients), and the recent emergence of multidrug resistant pathogens (Raghavan 2004). Similarly, the prevalence of SSSIs is difficult to track.

However, in the hospital setting, surgical site infections represent a significant source of SSSI/SSSIs. Although the incidence of in-patient surgical site infections varies by surgical category and between hospitals, 1.5% of reported surgical procedures resulted in infection from 2004 to 2005 in Scotland (Scottish Surveillance of Healthcare Associated Infection Programme report, 2005). Over a 6-year period, 4351 infections resulted from 149,745 surgical procedures in English hospitals, ranging from 2.2% for total hip replacements to 14.9% for limb amputation (Nosocomial Infection National Surveillance Service, 2004).

The etiological microbes in complicated SSSI are predominately *S. aureus*, *S. pyogenes*, *S. agalactiae*, and group C and G streptococci, but often involve mixed Gram-positive and Gram-negative aerobic and anaerobic bacteria as well (DiNubile 2004). *S. aureus* is by far the most common Gram-positive pathogen implicated in SSSI. Antimicrobial surveillance studies (1997–2000) conducted in hospitalized patients across Europe, US, Canada, Latin America, South Africa, and Asia-Pacific regions found that *S. aureus* accounted for almost half of isolates from SSSIs (Bell 2002; Diekema 2001; Fluit 2001a; Jones 1999; Rennie 2003). A similar proportion was noted in a recent surveillance study of inpatients representing nosocomial or hospitalized community-acquired skin, soft tissue, and wound infections. *S. pyogenes* has also been implicated in complicated SSSI/SSSI, and to a lesser extent Group B beta-hemolytic streptococci (Fluit 2001b; Stevens 2004; Swartz 2005).

MRSA has become a major concern, not just with respect to nosocomial infections, but also because a community-acquired (CA) variant has appeared, unrelated to the hospital acquired strains (Salgado 2003; Daum 2007). Most community-acquired MRSA (CA-MRSA) strains produce SSSIs, which include abscesses and cellulitis (Gorak 1999). Nevertheless, necrotizing infections and fatal pneumonias have also been described (Lina 1999; Klevens 2007). CA-MRSA is now the most common cause of CA soft tissue infections at major clinical care centers in the US (Moran 2005; Daum 2010; Landrum 2012) and in the EU (Huijsdens 2006). Furthermore, infection by MRSA has been associated with a poor clinical outcome as compared to that with methicillin-susceptible isolates (Engemann 2003; Melzer 2003). This changing epidemiology includes MRSA and other Gram-positive pathogens with reduced susceptibility such as other staphylococci, streptococci, and enterococci, and is global in scope, which has led to an increasing need to administer IV antibacterial agents with a spectrum of activity targeted for the empirical treatment of ABSSSI in a hospital and/or clinic setting (Diekema, 2004; Jones 2003; Moellering 2006; Abrahamian 2008). Some such infections, eg, *S. aureus* bacteremia, are associated with worse outcomes when due to MRSA compared to MSSA (Cosgrove 2004). Infections acquired in the community (including SSSIs) may also be caused by MRSA which encode for virulence factors associated with severe illness.

Accordingly, a medicinal agent with clinical efficacy against Gram-positive pathogens, including MRSA and CA-MRSA, a favorable benefit/risk ratio, and a favorable PK profile allowing convenient dosing in inpatients and outpatients with the potential for minimizing patient noncompliance and the risk of pain and discomfort and infection from multiple venipunctures or indwelling venous catheters would be a valuable addition to the antibacterial armamentarium for the treatment of ABSSSI/cSSSI.

9.2 Benefits Versus Risks of Dalbavancin Treatment in ABSSSI

Like other members of the glycopeptide class of antibiotics, dalbavancin binds to the terminal D-alanyl-D-alanine (D-ala-D-ala) of the stem peptide in nascent bacterial peptidoglycan, inhibiting cross-linking of bacterial cell wall components and therefore interfering with bacterial cell wall synthesis. Dalbavancin has activity against important groups of Gram-positive bacteria, including strains of MRSA that are also resistant to other classes of antibiotics. It has greater potency in vitro than most other antibiotics used to treat Gram-positive bacterial infections, and it has also demonstrated in vivo activity in a number of infection models, using both immunocompetent and immunocompromised animals.

9.2.1 Clinical Efficacy

The in vitro potency of dalbavancin, together with the extended $t_{1/2}$, has permitted the conduct of phase 2/3 clinical trials utilizing a once-weekly 2-dose regimen, and this has translated into demonstrable efficacy relative to standard comparators that must be administered at least twice daily for 10 or more days to achieve similar therapeutic effects. Dalbavancin met the primary non-inferiority endpoint in multiple studies when tested against appropriate comparators in relevant indications and patient populations. Such efficacy was durable.

9.2.2 Clinical Safety

Safety and tolerability were acceptable and comparable to each of the comparators separately and overall. No compound-specific or unique toxicity was identified, and, overall, the duration of AEs was similar to that of comparators. Safety in relevant subpopulations, such as the elderly and diabetic patients, was demonstrated. No dose-limiting toxicity was reached in phase 1 dose-escalation studies. A maximum tolerated dose was not identified. Drug-drug interactions were not demonstrated. There is no evidence of a QT effect. Hepatic safety was comparable to that of marketed comparators. There is no clear evidence that the administration of dalbavancin is causally related to an increased risk of hepatobiliary events. Importantly, the PK profile is characterized by very low interpatient variability and

predictable concentrations; therefore, therapeutic drug monitoring is not required. There are no known drug interactions with dalbavancin. The once-weekly dosing regimen, a simpler regimen than multiple-times daily IV dosing, provides convenience for patients, avoids the potential pitfalls of noncompliance with oral medication, and provides the possibility for earlier discontinuation of IV access, with its attendant risks of line-related thrombosis and infection. There is no requirement for an oral formulation to allow step- down therapy.

Dosing adjustment is not needed for most special populations; for severe renal insufficiency, a clear dosing guideline has been provided.

In phase 1 studies in healthy volunteers, dalbavancin administered at single doses or treatment regimens exceeding that of the recommended human therapeutic regimen did not result in additional adverse effects, suggesting that accidental overdose does not pose a significant risk.

There is unlikely to be any specific, clinically relevant concern about operating machinery or driving, other than the caution that should be exercised by any ill patient.

There are no adequate and well-controlled studies regarding the use of dalbavancin in pregnant women. Dalbavancin is excreted in the milk of lactating rats. It is not known whether dalbavancin is excreted in human breast milk.

Post-marketing surveillance for adverse events as well as in vitro microbiologic surveillance studies wil be conducted in order to monitor for any change in the exisiting benefit-risk profile.

9.2.2.1 Comparison with Approved Antibacterial Therapeutics

Approved alternatives for the treatment of ABSSSI caused by Gram-positive pathogens that were available during the clinical development program include vancomycin, telavancin, anti-staphylococcal penicillins, anti-staphylococcal cephalosporins, quinupristin/dalfopristin, linezolid, daptomycin, teicoplanin (non-US only) and tigecycline. A comparison of important features from product labeling and other sources reveals the following:

- Vancomycin (Vancomycin package insert, Jan 2012) has a well-established safety profile with decades of use in the US. Its use is associated with Red-Man syndrome (exfoliative dermatitis), infusion site reactions, rare ototoxicity, rare nephrotoxicity, and the requirement for therapeutic drug monitoring and twice daily dosing.
- Telavancin (Vibativ® package insert, June 2013) is also relatively well-tolerated, although it has been associated with new onset or worsening of renal impairment requiring the monitoring of renal function in all patients; decreased efficacy with moderate/severe Baseline renal impairment; infusion-related reactions requiring administration over at least 60 minutes to minimize infusion-related reactions; QTc prolongation; and interference with some laboratory coagulation tests, including prothrombin time, international normalized ratio, and activated partial thromboplastin time.
- The anti-staphylococcal penicillins (eg, oxacillin package insert, Sep 2012), while widely used and established as efficacious, lack activity against MRSA, an important pathogen in ABSSSI. Usage has been associated with infusion site reactions; rare ototoxicity; hypersensitivity reactions; rare jaundice/hepatic dysfunction; occasional myelosuppression, beta-lactam allergies, and the requirement for dosing 4–6 times daily.
- The anti-staphylococcal cephalosporins require multiple daily regimens and are not active against MRSA. Ceftaroline (Teflaro® package insert, Dec 2013), recently approved in the US and Europe, does have activity against MRSA. It is dosed intravenously twice daily and has been associated with hypersensitivity reactions.
- Quinupristin/dalfopristin (Synercid® package insert, Aug 2010) requires administration via central venous catheter, and is associated with frequent myalgias/ arthralgias, poor injection site tolerability, occasional hyperbilirubinemia, CYP450 drug-drug interaction potential, and multiple daily dosing regimens.

- Linezolid (Zyvox® package insert, May 2013), approved for marketing in the US in 2000, is a reversible, nonselective inhibitor of monoamine oxidase reactions, and has been associated with myelosuppression (thrombocytopenia, dose and duration-dependent); rare lactic acidosis; and rare neuropathy with prolonged therapy. Linezolid requires twice daily dosing.
- Daptomycin (Cubicin® package insert, Jan 2013) is a relatively new agent approved for cSSSI with activity against MRSA, and has been shown to cause rare muscle toxicity with higher and more frequent dosing.
- Teicoplanin (Targocid® Summary of Product Characteristics, April 2010) has been approved in the EU for the treatment of moderate to severe infections due to Gram-positive bacteria, including SSSIs, but is not approved in the US. Teicoplanin is less toxic than vancomycin, and is generally well-tolerated. However, unlike dalbavancin, it requires daily (or twice daily) administration and dose reduction in haemodialysed patients. Additionally, it must be used with care in conjunction with or sequentially with, other drugs with known nephrotoxic or ototoxic potential. Thrombocytopenia has been reported with teicoplanin.
- Tigecycline (Tygacyl® package insert, October 2013), has also become available for the treatment of cSSSIs. Like teicoplanin, tigecycline requires twice daily dosing. It is less well-tolerated, being very commonly associated with nausea (35%) and vomiting (20%). An increase in all-cause mortality has been observed across phase 3 and phase 4 clinical trials in tigecycline-treated patients versus comparator. Hepatic dysfunction and liver failure as well as pancreatitis have been reported and lower cure rates and higher mortality were seen when patients with ventilator-associated pneumonia were treated with tigecycline.

9.3 Conclusions from Clinical Studies

The antibacterial potency of dalbavancin against Gram-positive pathogens associated with ABSSSI and its long β half-life (8.5 days) contribute to the ability to offer a complete course of therapy with 2 weekly IV infusions totaling 1500 mg. Bactericidal potency is sustained throughout the treatment period. Compared to other marked glycopeptide antibacterials, and most other parenteral antibiotics in general, dalbavancin offers a convenient treatment regimen that allows for shortened hospital stays or fully-outpatient treatment, with less risks and discomfort associated with daily multiple infusions of other glycopeptide antibacterial agents with half-lives measured in hours, as opposed to days. No evidence of reduced susceptibility has been demonstrated with dalbavancin.

The available clinical safety and efficacy data for dalbavancin are robust. The size of the safety database is substantial for a parenteral product, although rare events cannot be excluded and safety will continue to be monitored in ongoing clinical trials and in postmarketing pharmacovigilance. Administration of single and multiple doses in excess of the proposed therapeutic regimen to healthy adult volunteers did not demonstrate any additional safety risk.

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Appendix 1 US Department of Health and Human Services, US Food and Drug Administration (FDA). Center for Drug Evaluation and Research, *Guidance for Industry: Acute bacterial skin and skin structure infections: Developing drugs for treatment* (Aug 2010)

Guidance for Industry

Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Joseph Toerner, MD, MPH at 301-796-1300.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2010
Clinical/Antimicrobial
Revision 1

Guidance for Industry

Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Antimicrobial
Revision 1

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Guidance for Industry[1]
Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of acute bacterial skin and skin structure infections (ABSSSI), impetigo, and minor cutaneous abscesses. Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for systemic drugs to support an indication for treatment of ABSSSI, and topical or systemic drugs to support an indication for treatment of impetigo or minor cutaneous abscesses.[2] This guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogen and Transplant Products, pharmaceutical sponsors, the academic community, and the public.[3] This guidance does not address lower extremity infections in neurologically compromised patients, such as the *diabetic foot infection* or *pressure sore infection*. Currently, there are ongoing efforts in the scientific community regarding clinical trial designs and endpoints for ABSSSI. As the science of clinical trial design for this indication evolves, we expect that this guidance may be revised.[4]

[1] This guidance has been prepared by the Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogen and Transplant Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the divisions to discuss specific issues that arise during drug development.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

This guidance revises the draft guidance for industry *Uncomplicated and Complicated Skin and Skin Structure Infections — Developing Antimicrobial Drugs for Treatment* published in 1998. Once final, this guidance will be considered the FDA's current thinking regarding the development of drugs to treat ABSSSI. It also supersedes, with regard to development of drugs to treat ABSSSI, more general guidance issued many years ago (i.e., *Clinical Evaluation of Anti-Infective Drugs (Systemic)* and *Clinical Development and Labeling of Anti-Infective Drug Products*, as well as the joint FDA/Infectious Disease Society of America's *General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products*).[5]

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*. This guidance focuses on specific drug development and trial design issues that are unique to the study of ABSSSI.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In general, the majority of skin infections are caused by Gram-positive bacteria such as *Streptococcus pyogenes* and *Staphylococcus aureus*. Methicillin-resistant *Staphylococcus aureus* (MRSA) is also an important pathogen in skin and skin structure infections. Because broad categories of skin infections tend to share common bacterial pathogens, clinical trials include several clinical disease entities under one or more general categories. Over the past several decades, skin infections have been characterized into two broad categories: (1) uncomplicated skin and skin structure infections (uSSSI); and (2) complicated skin and skin structure infections (cSSSI) with the synonym of skin and soft tissue infections also being used.

Since the 1998 draft guidance published, there have been public discussions about the definitions of skin and skin structure infections included in the general categories of uSSSI and cSSSI, clinical trial designs, and endpoints used in support of anti-infective drugs approved for the indications of the treatment of uSSSI and/or cSSSI. Many issues were discussed at the Anti-Infective Drugs Advisory Committee (AIDAC) meeting in November 2008.[6] These discussions have focused on clinical trial designs for ABSSSI and other important issues such as the following:

[5] Beam, TR, DN Gilbert, and CM Kunin, 1992, General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products, Infectious Disease Society of America and the Food and Drug Administration, Clinical Infectious Diseases, Nov.15, Supplement 1:S5-32.

[6] The Anti-Infective Drugs Advisory Committee meeting, November 18, 2008. Transcripts and briefing information can be found at the FDA Web site at http://www.fda.gov/ohrms/dockets/ac/cder08 html#AntiInfective.

- Definitions of skin and skin structure infections
- Noninferiority versus superiority design
- Justification of an appropriate noninferiority margin
- Enrollment criteria
- Time point of the primary efficacy outcome assessments

Based on these discussions and data available from clinical trials of antibacterial drugs, the types of skin infections that should be included in clinical trials to support an indication for treatment have been re-evaluated and are termed *acute bacterial skin and skin structure infections*. In addition, there are ongoing efforts in the scientific community to develop and evaluate new efficacy endpoints for ABSSSI that are assessed at an earlier time point than endpoints used in previously conducted trials. Important changes from the 1998 draft guidance that are based on these discussions have been incorporated into the appropriate sections below, including the definitions of ABSSSI and the proposed primary efficacy endpoints.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Definitions of Acute Bacterial Skin and Skin Structure Infection

The definitions of the clinical disease entities are based on the types of infections commonly encountered in clinical trials of skin and skin structure infections. The definitions of ABSSSI apply to enrollment criteria for enrolling adults and adolescents in clinical trials and are intended to support an indication for the treatment of ABSSSI. Therefore, they may differ in some respects from the treatment guidelines or other clinical decision tools for consideration of antibacterial drug therapy. The definitions of ABSSSI for use in enrollment criteria for children will vary, depending on the total body surface area of the pediatric populations targeted for enrollment. The definitions are divided into two general categories: (1) ABSSSI for which a reliable estimate of a treatment effect of antibacterial drug therapy can be described and either noninferiority or superiority trial designs are recommended; and (2) milder skin infections for which a treatment effect of antibacterial drug therapy has not been characterized and superiority trial designs are recommended.

(1) ABSSSI for which a reliable estimate of a treatment effect of antibacterial drug therapy can be described and either noninferiority or superiority trial designs are recommended:

– **Cellulitis/erysipelas:** A diffuse skin infection characterized by spreading areas of redness, edema, and/or induration of a minimum surface area of 75 cm^2 (e.g., length of 15 cm and width of 5 cm), accompanied by lymph node enlargement or systemic symptoms such as fever greater than or equal to 38 degrees Celsius (or 100.4 degrees Fahrenheit)

- **Wound infection:** An infection characterized by purulent drainage from a wound with surrounding redness, edema, and/or induration of a minimum surface area of 75 cm^2 (e.g., the shortest distance of redness, edema, and/or induration extending at least 5 cm from the peripheral margin of the wound), accompanied by lymph node enlargement or systemic symptoms such as fever greater than or equal to 38 degrees Celsius

- **Major cutaneous abscess:** An infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration of a minimum surface area of 75 cm^2 (e.g., the shortest distance of redness, edema, and/or induration extending at least 5 cm from the peripheral margin of the abscess), accompanied by lymph node enlargement or systemic symptoms such as fever greater than or equal to 38 degrees Celsius

- **Burn infection:** An infection characterized by purulent drainage, redness, edema, and/or induration of a minimum surface area of 75 cm^2 (e.g., the shortest distance of redness, edema, and/or induration extending at least 5 cm from the peripheral margin of the burn infection), accompanied by lymph node enlargement or systemic symptoms such as fever greater than or equal to 38 degrees Celsius

The hallmark of these definitions is the minimum surface area of redness, edema, and/or induration (i.e., 75 cm^2 of cellulitis). The reason for this is as follows: (1) it provides a patient population for which the treatment effect of antibacterial drug therapy would be expected to be similar to the treatment effect observed in historical studies of cellulitis/erysipelas; and (2) it provides an extent of disease to clearly and objectively document the infection and to follow clinical improvement or deterioration. We recommend that the ABSSSI clinical trial population include patients with a mixture of the clinical disease entities defined above. Because surgical incision and drainage might influence treatment outcomes among patients with major cutaneous abscesses, we recommend that patients with major cutaneous abscesses should not comprise more than 30 percent of the clinical trial population (note that major cutaneous abscess includes patients with a minimum surface area of surrounding redness, edema, and/or induration of 75 cm^2).

Patients with infections such as infections of animal or human bites, necrotizing fasciitis, diabetic foot infection, decubitus ulcer infection, myonecrosis, ecthyma gangrenosum, and catheter-site infections should not be enrolled in ABSSSI clinical trials. The treatment regimens for these infections are usually more complex than the treatment regimens provided in the context of an ABSSSI clinical trial. Sponsors who wish to develop a drug for one or more of these indications should consult with the FDA.

(2) Definitions for adults and children with milder skin infections for which a superiority trial design is recommended:

- **Minor cutaneous abscess:** An infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration of less

than 5 cm from the peripheral margin of the abscess for adults and adolescents and is not accompanied by systemic symptoms. The maximum size of the minor cutaneous abscess for use as enrollment criteria for children younger than approximately 13 years of age depends on the total body surface area of the child that is enrolled. The definition of minor cutaneous abscess for this pediatric population should be discussed with the FDA during protocol development.

- **Impetigo:** A distinct skin infection characterized by multiple, erythematous, yellowish, or crusted lesions on exposed surfaces of the body.

2. Drug Development Population

The intended clinical trial population should include adults and children with ABSSSI, or with the milder skin infections of minor cutaneous abscesses or impetigo. Sponsors are encouraged to discuss pediatric drug development with the FDA early in the course of clinical development, including the potential extrapolation of adult efficacy data, appropriate pharmacokinetic studies in pediatric patients to support the selection of a dose, the pre-approval safety database in children, and as appropriate when children are included in clinical trials the definitions of ABSSSI in the pediatric population (e.g., the minimum surface area of redness, edema, and/or induration for each pediatric population subgroup based on total body surface area).

3. Efficacy Considerations

The goal of ABSSSI clinical trials should be to demonstrate an effect of antibacterial drug therapy on the clinical course of ABSSSI caused by commonly implicated bacterial pathogens such as *S. aureus* or *S. pyogenes*. At least two adequate and well-controlled trials that establish safety and efficacy should be conducted for treatment of ABSSSI. Either noninferiority or superiority trials are recommended for the indication of treatment of ABSSSI disease entities of cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection.

Previously conducted clinical studies were examined to evaluate the natural history of ABSSSI in the absence of antibacterial drug therapy and to estimate the effect of treatment of ABSSSI with an antibacterial drug. Two previously conducted published clinical studies were identified that included comparison of ultra-violet (UV) light therapy to therapy with a sulfonamide antibacterial drug.[7] The endpoints used in these previously conducted clinical studies (e.g., resolution of fever and cessation of spread of the lesion) were assessed at a number of time points during the first several days of therapy, including at 48 to 72 hours after initiation of antibacterial drug therapy (see the Appendix for a discussion about the historical studies). Given that these studies were conducted a number of years ago and that recent trials in skin infections have used other endpoints assessed at other time points, we recommend that before conducting a phase 3 trial using the endpoint of cessation of spread of redness, edema, and/or induration and resolution of fever at 48 to 72 hours, sponsors should perform additional developmental work (e.g., in a phase 2 trial) to develop how this endpoint will be measured, and to evaluate its performance.

[7] See reference numbers 1 and 2 in the references section at the end of this guidance.

The developmental work for the endpoint should incorporate assessment of the accuracy and reliability of the proposed lesion size measurement method(s) to help identify the best measurement method(s) to minimize potential errors in lesion size measurement. Sponsors can consider daily measurements of lesion size for the first 3 days of treatment as well as lesion size at end-of-therapy and other follow-up visits to better characterize a primary endpoint based on cessation of the spread of the lesion and other secondary endpoints that evaluate lesion size(s). In addition, it also can be valuable to evaluate the inclusion and exclusion criteria. Information to establish methods for endpoint assessment and evaluating its performance in the population of interest (e.g., response rate for a particular endpoint) can be important in planning and conducting phase 3 trials (e.g., for sample size calculations).

At least two adequate and well-controlled superiority trials are recommended for the indication of treatment of impetigo or treatment of minor cutaneous abscesses.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Designs, Populations, and Inclusion Criteria

Patients with cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection as defined in this guidance can be enrolled in a noninferiority trial using an active control. A superiority clinical trial using an active control also can be conducted; placebo-controlled trials are not recommended.

The following are recommended inclusion criteria:

- Clinical documentation of cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection

- Documentation of a minimum surface area of 75 cm^2 based on length and/or width of redness, edema, and/or induration as described in section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection

- Documented fever, defined as an oral or tympanic temperature greater than or equal to 38 degrees Celsius[8]

We recommend that patients with impetigo or minor cutaneous abscesses be enrolled in a superiority trial using the test antibacterial drug versus placebo or an active control.

[8] We reviewed the baseline patient temperatures from selected databases of cSSSI trials and found the proportions of patients with documented temperature greater than or equal to 38 degrees Celsius at baseline varied between approximately 30 percent to approximately 90 percent of clinical trial patients. Although we recommend the documentation of fever as an inclusion criterion based on the historical data, sponsors can choose to put forth proposals seeking to justify inclusion criteria that would not include documentation of fever. Additional developmental work may help to further define methods for assessing fever as a baseline inclusion criterion.

We recommend that general inclusion criteria include clinical documentation of impetigo or minor cutaneous abscess as defined in section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection.

2. General Exclusion Criteria

Recommended general exclusion criteria for all trials include the following:

- Any recent use of antibacterial drug therapy in a clinical trial designed to show noninferiority. We recommend exclusion of patients who received systemic or topical antibacterial drugs within 14 days of enrollment (or within a longer period of time for prior use of an antibacterial drug with a long half-life). However, patients who received prior antibacterial drug therapy can be eligible for clinical trial entry in certain situations:
  - The clinic notes or photographs objectively document the clinical progression of ABSSSI (i.e., not by patient history alone)
  - Patients received a single dose of a short-acting antibacterial drug 3 or more days before clinical trial enrollment (e.g., administration of a single dose of an antibacterial drug for surgical prophylaxis)
  - Patients recently completed a treatment course with an antibacterial drug for an infection other than ABSSSI and the drug does not have antibacterial activity against bacterial pathogens that cause ABSSSI
- Patients with medical conditions that would alter the interpretation of a primary endpoint, such as patients with neutropenia or compromised immune function.
- Patients with suspected or confirmed osteomyelitis.
- Patients with suspected or confirmed septic arthritis.
- Patients with complex skin infections, such as diabetic foot infections. (Patients with diabetes and ABSSSI, for example cellulitis, can be enrolled into ABSSSI trials).
- Chronic use of an antipyretic drug (e.g., daily use of naproxen).

3. Clinical Microbiology Considerations

Because MRSA is an important pathogen in ABSSSI, a sponsor developing a drug for ABSSSI should assess activity against MRSA in nonclinical studies and in phase 1 and phase 2 clinical trials. The phase 3 clinical trials should include patients with MRSA.

An adequate clinical specimen for microbiologic evaluation should be obtained from all patients and sent to the laboratory for microscopic evaluation (e.g., Gram stain), culture, and in vitro antibacterial susceptibility testing performed on appropriate organisms isolated from the

specimen. Specimens should be processed according to recognized methods.[9] If the specimen is kept at room temperature, the Gram stain should be performed and the specimen plated for culture within 2 hours from the collection time. Alternatively, these tests can be performed within 24 hours of collection if the specimen is stored at 2 to 8 degrees Celsius before processing. The specimen for microscopic evaluation (e.g., Gram stain) and culture should be collected before administration of antimicrobial therapy and can be obtained by any one of the following means:

- A punch biopsy or aspirate of the leading edge of redness for patients with cellulitis/erysipelas

- Biopsy, needle aspiration, or surgically obtained specimens of purulent material from an infected wound or burn (a swab is not recommended)

- Using sterile techniques that minimize potential isolation of normal skin flora, aspiration of purulent material from a cutaneous abscess

In ABSSSI trials that enroll patients with cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection as described in this guidance, aerobic and anaerobic blood cultures at two separate sterile venipuncture sites are recommended before initiation of investigational drug therapy.

All isolates considered to be possible pathogens taken from patients enrolled in clinical trials should be saved in the event that additional testing of an isolate is needed (e.g., pulse field gel electrophoresis for strain identification). Sponsors conducting clinical trials outside the United States should characterize the pathogen and describe similarities and differences among isolates identified in the United States. For microbiological assessment, the investigator should collect the following information:

- The anatomic location of where the specimen was obtained.

- The specimen identification number.

- A description of how the sample was obtained, processed, and transported to the laboratory.

- Data from in vitro susceptibility testing of the isolates to both the investigational drug and other antibacterial drugs that may be used to treat ABSSSI caused by the pathogens targeted by the investigational drug. In vitro susceptibility testing should be performed by using standardized methods unless otherwise justified.[10] Sponsors should describe the exact methodology used for susceptibility testing if a standardized method was not used.

[9] American Society for Microbiology, 2007, Manual of Clinical Microbiology, 9th edition.

[10] Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute, Wayne, PA.

- Characterization of virulence factors associated with the bacterial pathogens (e.g., Panton-Valentine Leukocidin-positive isolates of *S. aureus* or emm-types of *S. pyogenes*).

The use of rapid diagnostic tests to determine the presence of the bacterial pathogens should be discussed with the FDA before initiation of clinical trials.

4. Randomization, Blinding, and Stratification

Patients should be randomized for receipt of the trial drug at enrollment. All trials should be multicenter, well-controlled, and double-blind unless there is a compelling reason for single-blind or open-label trials. If trials are single-blind or open-label, sponsors should discuss potential biases with the FDA and how the biases will be addressed.

5. Choice of Comparators

Noninferiority clinical trials for the evaluation of treatment of ABSSSI should include an FDA-approved drug for cSSSI, ABSSSI, or an appropriate-related skin infection indication. In addition, we recommend that the comparator drug also be one recommended for use based upon current treatment guidelines. The dosages, regimens, and infusion rates in the labeling should be used. Placebo or an antibacterial drug that is FDA-approved for the condition studied should be used for clinical trials of patients with minor cutaneous abscess or impetigo designed for superiority.

6. Prior Antibacterial Drug Therapy

In general, patients who have received prior effective antibacterial drug therapy for ABSSSI should not be eligible for enrollment into a clinical trial. If there is clinical documentation that the ABSSSI is progressing on the prior antibacterial drug therapy (i.e., persistent fever, progression of redness, edema, and/or induration from cellulitis, increased amounts of pus from the wound infection), a patient can be eligible for clinical trial enrollment. If the clinical trial includes patients with ABSSSI who progress despite antibacterial drug therapy, we recommend limiting the enrollment of these patients and the results should be evaluated in this subgroup to assess any potential effects of the prior antibacterial drug therapy on efficacy outcomes.

7. Concurrent Antibacterial Drug Therapy

In general, concurrent antibacterial drugs should not be administered in the trial to evaluate the efficacy of the test antibacterial drug versus the control. Certain patients with ABSSSI may require broad spectrum antibacterial coverage that is beyond the antibacterial activity of the test drug or control drug. To the extent possible, any additional antibacterial drug to provide a broad spectrum antibacterial coverage should not have overlapping antibacterial activity with the test drug.

Other infections can occur in patients being treated for ABSSSI, and enrollment in a trial should not preclude treatment of other infections. However, the use of other concurrent antibacterial drug therapy will confound efficacy results and should be considered a clinical failure in the primary analysis populations, unless there is documentation that the nontrial antibacterial drug does not demonstrate activity in the treatment of ABSSSI.

8. Adjunctive Therapy

Adjunctive therapy is often used in ABSSSI treatment, including the following:

- Daily dressing changes
- Use of topical solutions including nonspecific antimicrobial drugs such as povidone-iodine
- Debridement
- Hyperbaric oxygen treatments
- Surgical interventions planned at the initiation of treatment

Sponsors should specify which adjunctive therapies are to be permitted in the clinical trials. With proper blinding and randomization, both the investigational drug group and the active-control drug (or placebo) group should have comparable use of these adjunctive therapies. Sponsors should analyze the clinical outcomes stratified by the presence or absence of adjunctive therapies (e.g., daily debridement). We recommend that topical treatments with specific antibacterial activity should not be used as adjunctive therapy in ABSSSI clinical trials.

Many patients will take systemic antipyretic drugs for relief of clinical symptoms associated with fever (e.g., chills, warmth). For patients enrolled in clinical trials, oral or tympanic temperature should be recorded every 6 hours or 4 times per day during the first 3 days of therapy. If the temperature is greater than 38 degrees Celsius, the patient may take a short-acting antipyretic drug for relief of symptoms associated with fever. If the patient takes a short-acting antipyretic drug for each episode of fever and does not take an antipyretic drug in the absence of fever, consecutive temperature recordings of the resolution of fever would be attributable to the effect of the antibacterial drug. The resolution of fever would not be attributed to the antipyretic drug because, in the absence of fever, an antipyretic drug would not have been taken.

For example, if a patient takes one dose of acetaminophen for each temperature recording of greater than 38 degrees Celsius during the first 36 hours of therapy, and then has temperature recordings of less than 37.7 degrees Celsius during 48 to 72 hours and an antipyretic drug is not taken, the resolution of fever at 48 to 72 hours can be attributed solely to the effect of the antibacterial drug. With this approach of taking one dose of a short-acting antipyretic drug only in the event of a fever, consecutive temperature recordings of less than 37.7 degrees Celsius would not be influenced by antipyretic drugs. For relief of pain, analgesic drugs without antipyretic activity should be used. Alternatively, protocols should provide an algorithm for use of drugs for relief of pain that ensures the endpoint of resolution of fever is attributed solely to the effect of the antibacterial drug without the influence of an analgesic drug.

9. Efficacy Endpoints and Timing of Assessments

We recommend a responder variable for clinical outcome at 48 to 72 hours as the primary endpoint based on the timing of efficacy endpoints in the historical studies that were used to support a noninferiority margin (see the Appendix). As stated in section III.A.3., Efficacy Considerations, before initiating phase 3 clinical trials sponsors should develop a standardized method to assess this endpoint and evaluate its performance in phase 2 clinical trials. Some of the issues to be addressed in phase 2 clinical trials pertain to the lack of clarity regarding the clinical observations early in the course of treatment for ABSSSI. For example, because of the rapid spread of redness, edema, and/or induration in some patients at the time of presentation with ABSSSI, the lesion may continue to spread during a short period of time after administration of the first doses of antibacterial drug therapy. Because events that occur after randomization and may be influenced by trial drug have potential to bias treatment effects, comparison to the lesion documented at trial entry (baseline) is recommended. Phase 2 trials and phase 3 clinical trials should plan to follow patients for the duration of therapy and for a period of observation after completion of therapy.

Primary efficacy endpoint and timing of assessments for a noninferiority trial in ABSSSI (clinical response or clinical failure at 48 to 72 hours):

- *Clinical response:* Cessation of the spread of the redness, edema, and/or induration of the lesion or reduction in the size (length, width, and area) of redness, edema, and/or induration at 48 to 72 hours after enrollment *and* resolution (absence) of fever (i.e., temperature less than 37.7 degrees Celsius at 3 consecutive recordings by the same methodology every 6 hours between 48 and 72 hours)

- *Clinical failure:* Death; continued fever (i.e., temperature greater than or equal to 37.7 degrees Celsius); increase in the size (length, width, and area) of redness, edema, and/or induration of the lesion; or administration of rescue antibacterial drug therapy or administration of nontrial antibacterial drug therapy for treatment of ABSSSI before the primary efficacy endpoint assessment

Secondary efficacy endpoints and timing of assessments for a noninferiority trial in ABSSSI:

Patients should be evaluated for continued clinical improvements and sustained clinical response for the duration of antibacterial drug therapy and for a period of observation after completion of antibacterial drug therapy. These evaluations for important secondary efficacy endpoints can be useful for the determination of overall evidence of efficacy. The clinical evaluation of patients and the timing of the secondary efficacy endpoints should be considered to ensure that clinical improvement can be objectively documented, recognizing that patients will still have signs or symptoms that may require additional time to completely resolve. The secondary outcome definitions and the timing of assessments are as follows:

- *Clinical response:* Cessation of the spread of the lesion at 48 to 72 hours, and resolution of the infection at 10 days post-randomization and at additional follow-up visits following completion of therapy

- *Clinical failure:* Protocols should prospectively define clinical failures at 48 to 72 hours, at a fixed time point 10 to 14 days post-randomization, and at additional follow-up visits, and should include but may not be limited to the following:

  – Deaths (all-cause mortality) from the start of trial drug

  – Incision and drainage of the ABSSSI site that was not planned before randomization or specified in the protocol[11]

  – Persistent purulent drainage (for a duration of at least 48 hours) from a wound infection at the same or greater intensity as enrollment

  – Initiation of rescue antibacterial drug treatment or initiation of nontrial antibacterial drugs for treatment of ABSSSI

  – Initiation of nontrial antibacterial drugs for treatment of any other infection unless there is documentation that the nontrial antibacterial drug does not demonstrate activity in the treatment of ABSSSI

  – Patients who otherwise do not meet the definition of clinical success

Patients designated as clinical failures for the primary efficacy endpoint at 48 to 72 hours yet overall show clinical signs of improvement (e.g., cessation of spread of the lesion and decrease in temperature from 39.2 degrees Celsius to 37.9 degrees Celsius) can remain on the assigned treatment and can be counted as a clinical response at the secondary efficacy endpoint at a fixed time point 10 to 14 days post-randomization. If patients are clinical responders at the primary endpoint assessment at 48 to 72 hours, and are then offered rescue therapy after this assessment (see section III.B.10.f., Rescue therapy), those patients should be counted as clinical failures at the secondary efficacy endpoint that evaluates sustained clinical response at the fixed 10- to 14-day time point after randomization.

Additional important secondary analyses should include absolute and percent change from baseline in the reduction of the lesion size (length, width, and area) at 48 to 72 hours and at the post-therapy visits. The following are additional considerations for the timing of secondary endpoints:

- *Visit (fixed time point 10 to 14 days post-randomization):* This visit should be the trial visit at trial day 10 to 14 post-randomization to evaluate *clinical response* or *clinical failure* as secondary efficacy endpoints. In general, the administration of antibacterial

[11] Sponsors should provide documentation of the surgical operative notes.

drug therapy for treatment of ABSSSI and a clinical decision to discontinue antibacterial drug therapy based on clinical response should be completed by the 10-day time point.

- *Follow-up post-therapy visits:* These trial visits should evaluate the maintenance of clinical response after completion of therapy (e.g., trial days 21 to 28 post-randomization). Sponsors should use a prospective definition of clinical failures at follow-up visits, outlined above in *Clinical failure*. For drugs that have evidence of prolonged tissue levels, the sponsor should propose appropriate timing for follow-up visits after completion of therapy.

  Note: These important secondary endpoints are intended to assess the robustness of the overall evidence and consistency of treatment effect. However, if sponsors intend to pursue efficacy claims based on a superiority hypothesis of these secondary endpoints, then the analysis should be prespecified that, control the family-wise type I error rate, and the findings replicated in at least two clinical trials. The analysis plan should be discussed with the FDA before trial initiation.

Patient-reported outcome measures in ABSSSI:

Use of a patient-reported outcome (PRO) instrument is advised when measuring aspects of disease (or its treatment) that are best measured from the patient perspective (e.g., pain intensity). A PRO measure designed to capture the important symptoms of ABSSSI can be considered a direct measure of treatment benefit and can be used in a superiority trial to support labeling claims. Development of a new instrument should begin well in advance of phase 3 clinical trials so that the instrument can be qualified as well-defined and reliable at the time it is incorporated into the phase 3 protocol. The use of a PRO measure may have limited utility as a primary efficacy endpoint in a noninferiority trial of ABSSSI because of the difficulty in estimating a treatment effect over placebo based on a PRO measure. The use of a PRO measure as a secondary or exploratory endpoint in phase 3 noninferiority trials may help to characterize its usefulness as an efficacy endpoint in future trials.[12]

Primary efficacy endpoint of clinical success for a superiority clinical trial in impetigo or minor cutaneous abscess:

We recommend a fixed time point at the completion of investigational drug therapy (see section III.B.10.c., End-of-therapy visit) for the objective assessment of clinical resolution of impetigo or minor cutaneous abscess.

10. Trial Procedures and Timing of Assessments

a. Entry visit

[12] For more information, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

At the entry visit, the following information at a minimum should be obtained and recorded on the case report form:

- History and physical examination
- Underlying medical conditions (e.g., diabetes mellitus) and drug allergies
- Previous medical or surgical therapies for the infection being studied
- Baseline signs and symptoms of ABSSSI (or impetigo or minor cutaneous abscess)
- Vital signs and record of temperature with method of measurement to be consistent among individuals throughout the trial (e.g., oral temperatures throughout the clinical trial)
- The extent of the infection (e.g., measurements of width and length) documented at or near the time of the first administration of clinical trial drug therapy
- Cause of the infection (e.g., traumatic wound, spontaneous abscess)
- Microbiological specimens obtained before administration of antibacterial drug therapy: adequate clinical specimens for Gram stain and culture; blood cultures (aerobic and anaerobic) from two separate venipuncture sites obtained using sterile procedures
- Laboratory tests: hematology, chemistry, and other tests as appropriate
- Concomitant medications
- Optional standardized photography of the ABSSSI site; can be helpful for subsequent review

b. On-therapy visits during 72 hours following enrollment

The evaluations during the first 72 hours are of critical importance for the assessment of the primary endpoint. Patients should have recordings of temperature at least 4 times per day (e.g., every 6 hours) for 72 hours, which can be recorded on case report forms for hospitalized patients or recorded on patient diary cards in an outpatient setting (ensuring that patients are dispensed a thermometer and are instructed on methods for obtaining an accurate temperature (e.g., sublingual placement of the oral thermometer, oral temperature should not be obtained while consuming hot beverages)). The areas of redness, edema, and/or induration should be evaluated and the measurements and observations documented on a case report form at least once per day for 72 hours. This can be accomplished in the hospital setting or with daily visits to a clinic for the first 72 hours.

The 72-hour assessment should address the following:

- Review of adverse events

- Review of the recordings of oral or tympanic temperature taken every 6 hours (a consistent method of temperature measurement should be used in individual patients in the trial)

- Evaluation and measurements of the infection site (e.g., objective characterization of cessation of (or absolute and percent reduction in length, width, and area from baseline) the amount of redness, edema, and/or induration)

- Review of signs and symptoms of ABSSSI (or impetigo or minor cutaneous abscess)

- Administration of a PRO instrument (e.g., pain intensity by a validated pain scale), if used

- Completion of an abbreviated physical examination, as appropriate

- Performance of laboratory tests, as appropriate

- Review of concomitant medications including the use of analgesic or antipyretic drugs

- Record of planned and unplanned adjunctive therapies and operative notes

c. End-of-therapy visit

The end-of-therapy visit at the completion of investigational drug therapy should be used to evaluate the primary endpoint in trials enrolling patients with impetigo or minor cutaneous abscess. An end-of-therapy visit also can be incorporated into clinical trials of ABSSSI to assess whether discontinuation of antibacterial drug therapy is appropriate.

d. Visit at a fixed time point 10 to 14 days post-randomization

The post-therapy visit at a fixed time point 10 to 14 days post-randomization should be used to evaluate the secondary endpoint of clinical response or clinical failure. In general, this visit should correspond to the completion of therapy or within several days after completion of therapy and address the following:

- Review of adverse events
- Evaluation and objective measurements of the infection site and overall assessment as clinical response or failure
- Completion of physical examination including vital signs
- Performance of laboratory tests, as appropriate
- Review of concomitant medications
- Record of planned and unplanned adjunctive therapies

At the post-therapy visit, investigators should document findings from on-therapy office visits (e.g., history, physical examination, and laboratory test results) on the patient case report form. If the investigator contacted the patient by telephone or by another interactive technology, the investigator should capture on the case report form documentation of the specific questions asked, how they were asked, and the responses given by the patients. If a patient diary is used to capture patient symptoms during the trial, this information in the diary should also be collected at the post-therapy visit and recorded on the patient case report form.

e. Follow-up post-therapy visits

The evaluation of the maintenance of clinical response should occur at 1 or 2 weeks after completion of therapy (e.g., at trial day 21 to 28 post-randomization) and address the following:

- Review of medical history
- Review of adverse events
- Evaluation of the infection site and assessment as clinical response or failure
- Completion of physical examination
- Performance of laboratory tests, as appropriate
- Review of concomitant medications
- Record of planned and unplanned adjunctive therapies

It is important that all patients be followed for at least 28 days after enrollment to capture 28-day all-cause mortality data. If a follow-up post-therapy clinical trial visit for the evaluations as above is scheduled before the 28-day time point, the 28-day assessment can be performed by telephone contact or by another interactive technology in patients who were considered to be clinical successes and had no adverse events noted at or after the post-therapy visit. For patients with adverse events occurring at or after the post-therapy visit, investigators should perform an assessment that includes a medical history, physical examination, appropriate laboratory evaluations, and identification of any new adverse events. All adverse events should be followed until resolution.

f. Rescue therapy

It is important for investigators to distinguish patients who are worsening or not improving (i.e., where rescue antibacterial drug therapy is appropriate) from patients who are slow to improve but still may remain on assigned therapy and thereby achieve clinical success. As such, patients with ABSSSI who are characterized as clinical failures at the 48- to 72-hour primary endpoint assessment may not require rescue therapy if overall there appears to be slow clinical improvement on their assigned treatment. For patients who clearly and objectively are worsening or not improving and require rescue therapy, specimens for microbiological evaluation (see section III.B.3., Clinical Microbiology Considerations) should be obtained in these patients before initiation of the rescue antibacterial drug therapy. Patients who receive rescue antibacterial drug therapy should continue to have protocol-specified assessments identical to patients who continue to receive their originally assigned treatment.

11. Statistical Considerations

The trial hypothesis and the analysis methods should be stated in the protocol and/or the statistical analysis plan before initiation of the trial. The trial should be adequately powered to detect differences between treatment arms if differences exist. If sponsors choose to test multiple primary or secondary hypotheses, the statistical issues of the overall (family-wise) type 1 error rate and multiplicity should be discussed with the FDA during protocol development and should be incorporated into the statistical analysis plan.

a. Analysis populations

The definitions for the statistical analysis populations are provided as follows:

- Safety population — All patients who received at least one dose of drug during the trial.
- Intent-to-treat (ITT) population — All patients who were randomized.
- Microbiological intent-to-treat (MITT) population — All patients randomized to treatment assignment who have a baseline bacterial pathogen known to cause ABSSSI, impetigo, or minor cutaneous abscess. Patients should not be excluded from this population based upon events that occur post-randomization (e.g., lost to follow-up).
- Per-protocol or clinically evaluable population — Patients who meet the definition of ITT population and who follow important components of the trial as specified in the protocol.
- Microbiologically evaluable population — Patients who meet the definition of the MITT population and who follow important components of the trial as specified in the protocol.

For superiority trials, the ITT population should be considered the primary analysis population and the MITT should be considered a critical secondary analysis population. It is important to note that analyses of the per-protocol population and the microbiologically evaluable population are subgroup analyses because they exclude patients based on events that occur after randomization. However, consistency of the results should be evaluated on all populations.

For noninferiority trials, the ITT population should be considered the primary analysis population. The results based on a per-protocol population should closely correspond to the results based on the ITT population in a noninferiority trial, because missing information might result in biases toward a conclusion of noninferiority. For example, missing information counted as failures in an ITT population might bias the treatment groups to appear similar and the exclusion of patients after randomization in a per-protocol population might also bias the treatment groups to appear similar. There is no single way to deal with missing data and sponsors should make every attempt to limit loss of patients from the trial. There are several approaches to assess the robustness of the results based on missing observations and these methods should be specified in the protocol as additional analyses. Therefore, consistency of the results in all populations should be evaluated and any inconsistencies in the results of these analyses should be explored and explanations provided.

Based on the clinical trial population and the extent of antibacterial activity of the test drug and the control drug, there are other considerations for the analysis populations that sponsors may wish to discuss with the FDA. For example, an ABSSSI clinical trial population might include patients suspected of having either Gram-positive or Gram-negative pathogens, yet the test antibacterial drug being evaluated has activity against only Gram-positive pathogens and the protocol specifies that Gram-negative coverage may be added when Gram-negative infection is suspected or identified. Because the test antibacterial drug would not be expected to have activity against Gram-negative pathogens, analysis populations characterized by the type of infection (e.g., Gram-positive infections for an agent with Gram-positive activity) should be discussed with the FDA in advance of initiation of phase 3 clinical trials.

b. Noninferiority margins

Noninferiority trials are only appropriate and recommended if there is reliable and reproducible evidence of treatment effect for the comparator drug, based on historical studies for the proposed endpoint and patient population.[13] Noninferiority trials may be appropriate when enrolling patients with cellulitis/erysipelas, wound infection, major cutaneous abscesses, or burn infections as described in this guidance for the indication of ABSSSI (see the Appendix). Based on the evaluations of patients during the first 72 hours of therapy (as described in section III.B.10.b., On-therapy visits during 72 hours following enrollment), the recommendation for primary efficacy endpoint in a noninferiority clinical trial is the cessation of spread of the lesion and resolution of fever at 48 to 72 hours after initiation of clinical trial therapy, although there are no recent data available for validating the sensitivity of this endpoint compared to the historical evidence of treatment effect. The noninferiority margin described in the Appendix applies to a clinical trial that enrolls patients with ABSSSI definitions and disease spectrums defined in this guidance (see section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection). Sponsors should justify the noninferiority margin for the proposed trial design and population enrolled and discuss the justification of the margin with the FDA during clinical development. Superiority trials are recommended for the indications of the treatment of impetigo or minor cutaneous abscess.[14]

c. Sample size

The appropriate sample size for a clinical trial should be based on the number of patients needed to answer the research question posed by the trial. The sample size is influenced by several factors including the prespecified type I and type II error rates, the expected success rate, and the noninferiority margin, or the amount by which an investigational drug is expected to be superior

[13] See the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[14] Noninferiority clinical trial designs for skin and skin structure infections were discussed at the November 18, 2008, AIDAC meeting; the committee voted that the noninferiority trial design was not appropriate for specific *uncomplicated* skin infections including impetigo and minor cutaneous abscesses (see http://www fda.gov/ohrms/dockets/ac/cder08.html#AntiInfective).

(for a superiority trial). The appropriate sample size should be estimated using a two-sided type I error of 0.05 (α=0.05) and adequate statistical power (e.g., 80 percent or more).

d. Missing data

There is no single optimal way to deal with missing data from clinical trials. Sponsors should make every attempt to limit loss of patients from the trial. The methods of how missing data will be analyzed should be specified in the protocol. Higher proportions of missing data will limit the interpretability of the results as discussed in section III.B.11.a., Analysis populations.

e. Secondary endpoints and other analyses of interest

Sponsors should evaluate the secondary endpoint of clinical response and clinical failure at the post-therapy visit at a fixed time point 10 to 14 days post-randomization in noninferiority ABSSSI clinical trials. The robustness of the secondary efficacy data should be evaluated by comparing any differences among the results of the primary efficacy analysis at 48 to 72 hours post-randomization, and any differences should be thoroughly explored and explanations provided. Sponsors can present other secondary analyses on other endpoints of interest such as:

- Outcomes at other time points on therapy or after completion of therapy
- Mortality endpoints
- Outcomes between patients with bacteremia versus patients without bacteremia
- Response based on patient demographic characteristics, such as age, geographic region, underlying medical conditions, and microbiological etiology
- Response based on baseline microbiological confirmation
- Time to complete resolution of signs and symptoms of ABSSSI
- Clinical failures and relapses after the post-therapy visit
- Clinical responses by subgroups of ABSSSI (e.g., responses in patients with wound infections)

12. Accelerated Approval Considerations (21 CFR Part 314, Subpart H)

Currently, there are no surrogate markers recommended by the FDA as substituting for clinical outcomes in ABSSSI trials that would meet the criteria for accelerated approval under subpart H. Sponsors who wish to propose a surrogate marker for a clinical outcome should discuss this with the FDA early in the drug development process.

819 *13. Risk-Benefit and Ethical Considerations*
820
821 Risk-benefit considerations should depend on the populations being studied and the safety profile
822 of the drug being investigated. A noninferiority trial or superiority trial using an active-
823 controlled comparator drug in patients with ABSSSI can provide useful risk-benefit information
824 relative to an approved comparator drug.
825
826 Superiority trials are recommended for evaluation of drugs for treatment of impetigo or minor
827 cutaneous abscess.[15] Although there may be a small treatment effect attributable to antibacterial
828 drugs, impetigo and minor cutaneous abscesses are often self-limited infectious diseases with
829 nonantibacterial drug treatments (e.g., surgical incision and drainage for minor cutaneous
830 abscesses). Complications from impetigo or minor cutaneous abscesses are rare, and there were
831 no reports of serious complications among patients randomized to receive placebo in historical
832 clinical studies of impetigo or minor cutaneous abscesses. Antibacterial drugs have adverse
833 effects associated with their administration. Therefore, the overall risk to patients with impetigo
834 or minor cutaneous abscess receiving placebo may be similar to the overall risk to patients
835 receiving an antibacterial drug. Rescue antibacterial drugs can be administered (open-label) at
836 the time a nonresponder or failure endpoint is assigned as a measure to mitigate risk to patients
837 randomized to receive placebo. All trial designs should provide appropriate provisions for
838 patient safety.
839
840 **C. Other Considerations**
841
842 *1. Pharmacokinetic/Pharmacodynamic Considerations*
843
844 The pharmacokinetic/pharmacodynamic (PK/PD) characteristics of the drug should be evaluated
845 using in vitro models or animal models of infection if not previously performed. Before the
846 initiation of clinical trials, sponsors should identify the PK/PD index best associated with
847 antibacterial effect and the magnitude of the PK/PD index necessary to achieve the desired
848 endpoint. The results from PK/PD assessments should be integrated with the findings from
849 phase 1 PK assessments to help identify appropriate dosing regimens for evaluation in phase 2
850 and phase 3 clinical trials. We recommend a dose-response trial design as an option for early
851 clinical trials (e.g., phase 2 clinical trials) to weigh the benefits and risks when selecting doses
852 and ensure that suboptimal doses or excessive doses (beyond those that add to efficacy) are not
853 used, offering some protection against unexpected and unrecognized dose-related toxicity.
854
855 Sponsors should consider a sparse sampling strategy from all patients in phase 2 and phase 3
856 clinical trials to allow for the estimation of drug exposure in each patient. Collection of PK data
857 in phase 2 clinical trials can be used to explore the exposure-response relationship and to confirm
858 that the proper dosing regimen is selected for further evaluation in phase 3 clinical trials.
859 Collection of PK data in phase 3 clinical trials may help to explain potential questions regarding
860 efficacy or safety that might arise from the clinical trials.

[15] Noninferiority clinical trial designs for skin and skin structure infections were discussed at the November 18, 2008, AIDAC meeting; the committee voted that the noninferiority trial design was not appropriate for specific *uncomplicated* skin infections including impetigo and minor cutaneous abscesses (see http://www fda.gov/ohrms/dockets/ac/cder08.html#AntiInfective).

A retrospective exposure-response analysis based on the population PK model from patients in phase 3 clinical trials should be performed to assess the relationship between PK/PD indices and observed clinical and microbiologic outcomes. The relationship between drug exposure and clinically relevant adverse events should also be explored to identify potential risks with different dosing regimens (if applicable) and specific patient populations (e.g., patients with renal impairment).

2. Dose Selection and Formulations

The findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics, pharmacodynamics, in vitro susceptibility profiles of target pathogens, safety and tolerability information from phase 1 trials, and safety and antibacterial activity information from phase 2 dose-ranging trials should be integrated for purposes of selection of appropriate doses to be evaluated in phase 3 clinical trials. Nonclinical data should document activity against commonly implicated pathogens for ABSSSI. An assessment of drug penetration at the site of action (e.g., skin blister or microdialysis studies) can be used as supportive evidence that the selected doses are likely to achieve drug concentrations sufficient to exert both an antimicrobial and clinical effect. If appropriate, we recommend microdialysis in patients with ABSSSI because it minimally alters the integrity of skin and allows differences in drug concentrations between healthy subjects and infected patients to be considered. In addition, the pharmacokinetics of the drug in specific populations (e.g., pediatric patients, geriatric patients, patients with renal or hepatic impairment) should be evaluated before initiation of phase 3 clinical trials to determine whether dose adjustments are necessary. This may prevent the exclusion of such patients from phase 3 clinical trials.

For drugs that only have an intravenous (IV) formulation available, we recommend that clinical trials be conducted with the IV formulation alone without a switch to an oral antibacterial drug to allow for proper assessment of both efficacy and safety of the test drug. Patients do not need to be hospitalized to be enrolled and can receive the IV formulation of the drug as an outpatient.

For drugs that have both an IV and oral formulation, a switch to the oral drug may be appropriate provided that pharmacokinetics of the oral formulation have been adequately evaluated to ensure comparable exposure and to determine an appropriate dosing regimen. Appropriate clinical response criteria that allow for IV to oral switch should be specified in the clinical trial protocol.

If practice patterns allow, hospitalized ABSSSI patients can be enrolled in oral antibacterial drug trials. Appropriate criteria that allow for treatment with an oral drug should be specified in the protocol.

3. Other Clinical Microbiology Issues in Clinical Trials

If sponsors want to include less commonly implicated bacterial pathogens in clinical trials for ABSSSI, such as *Staphylococcus haemolyticu*s, *Streptococcus dysgalactiae*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, *Enterococcus faecalis*, or Gram-negative bacteria,

they should provide data sufficient to substantiate the clinical relevance of the particular bacterial pathogen in ABSSSI.

4. Safety Considerations

The protocols should specify the methods to be used to obtain safety data during the course of the clinical trials. Both adverse event information and safety laboratory data should be collected during the trial. All patients should be evaluated for safety at the time of each trial visit or assessment, regardless of whether the test drug has been discontinued. All adverse events should be followed until resolution, even if time on clinical trial would otherwise have been completed.

A sufficient number of patients including those older than 65 years and pediatric patients should be evaluated at the exposure (dose and duration) proposed for use to draw appropriate conclusions regarding drug safety.

5. Labeling Considerations

The labeled indication should be based on the types of patients enrolled in the clinical trials.

- For clinical trials enrolling patients with ABSSSI as defined in this guidance, the labeled indication should be for the treatment of ABSSSI caused by specific bacteria identified in patients in the clinical trials. The clinical disease entities studied for ABSSSI among the patients enrolled in the clinical trials should be reflected in the CLINICAL STUDIES section of labeling. For example:

  "Drug X is indicated for the treatment of acute bacterial skin and skin structure infections due to…."

- For clinical trials in patients with impetigo or minor cutaneous abscesses, the labeled indication should reflect the clinical disease entities in labeling. For example:

  "Drug X is indicated for the treatment of impetigo due to…."

APPENDIX: JUSTIFICATION FOR A NONINFERIORITY MARGIN FOR ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

Background

Acute bacterial skin and skin structure infections are common and encompass a variety of disease presentations and severity. A clinical trial design using an active-comparator antibacterial drug is recommended for the clinical disease entities of ABSSSI as defined in this guidance (i.e., cellulitis/erysipelas, wound infection, major cutaneous abscess, and burn infection). One type of trial design using an active-comparator is the noninferiority clinical trial using a prespecified noninferiority margin. The first step sponsors should consider for a noninferiority trial design is determining the treatment effect of the active-comparator drug that can be reliably distinguished from placebo (M1). This step is supported by evidence from previously conducted trials using reliable efficacy endpoints.[16] The results from previously conducted placebo-controlled trials, where the effect of a drug can be reliably distinguished from placebo, provide the strongest evidence for M1. When evaluating M1, the population in which the control drug was studied, the endpoint assessed, and the timing of assessment are critical factors in evaluating how the information on treatment effect derived from previously conducted trials might be applied in a future trial. This Appendix summarizes our efforts to identify a treatment effect of antibacterial drugs in the treatment of skin and skin structure infections.

A literature search was conducted to identify published articles that describe the effects of antibacterial drug treatment for skin infections. For the types of ABSSSI defined in this guidance (i.e., cellulitis/erysipelas, wound infection, major cutaneous abscess, and burn infection), there were no placebo-controlled trials in the historical literature. We identified two controlled studies that evaluated antibacterial drugs versus nonantibacterial treatments in patients with cellulitis/erysipelas. In addition, approximately 30 active-controlled or uncontrolled studies were available in the literature, but these studies did not help to identify a treatment effect over placebo. Finally, seven placebo-controlled studies of skin infections of a lesser severity (i.e., impetigo and minor cutaneous abscesses) were available in the literature.

Controlled studies in cellulitis/erysipelas

Two controlled studies were identified in the scientific literature that compared outcomes in patients with cellulitis/erysipelas treated with an antibacterial drug versus nonantibacterial drug therapy.[17] Investigators at Ruchill Hospital in Glasgow, Scotland, conducted two controlled clinical studies of patients admitted to their hospital ward with erysipelas. During the 1930s, the use of UV light was a *routine method employed in the hospital* because previous studies

[16] See the draft guidances for industry *Non-Inferiority Clinical Trials* and *Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval*. When final, these guidances will represent the FDA's current thinking on these topics. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

[17] See reference numbers 1 and 2 in the references section at the end of this guidance.

published in the mid-1930s showed potential benefit in erysipelas when compared to other nonantibacterial therapies. UV light therapy was the control group in these studies.

Both studies enrolled patients with clinically documented erysipelas; however, the identification of a bacterial pathogen was not reported among study patients. Erysipelas is a term often used to describe infections of the upper dermis, usually caused by *S. pyogenes*. Cellulitis is a term often used to describe skin infections deeper in the subcutaneous tissues. *S. pyogenes* and other pathogens including *S. aureus* have been identified as bacterial pathogens in cellulitis. Erysipelas and cellulitis can be difficult to distinguish clinically and physicians use either term to describe skin infections of the upper dermis or subcutaneous tissues. We inferred that these two studies enrolled patients with cellulitis/erysipelas (ABSSSI) caused by either *S. pyogenes* or *S. aureus*.

In the first study (Study 1), approximately 312 patients admitted from May 1936 to February 1937 received one of four open-label treatments for erysipelas:

- UV light
- Prontosil (a sulfonamide antibacterial drug that is metabolized to sulphanilamide)
- UV light plus Prontosil
- Scarlet fever antitoxin

In the second study (Study 2), approximately 270 patients admitted from February 1937 to August 1937 received one of two open-label treatments for erysipelas:

- UV light
- Sulphanilamide (a sulfonamide antibacterial drug)

The articles did not describe how patients were randomized, but stated that a statistician had reviewed the demographic characteristics and found that the groups appeared similar with regards to age, comorbid conditions (e.g., diabetes), and disease severity. The efficacy endpoints prespecified in the studies included the clinical observations of whether the "lesion continues to spread," the "temperature has become normal," and the patient "continues in a toxic condition." The authors stated that the duration of these clinical observations would be compared among the different treatment groups.

In Study 1, UV light treatments were administered daily "when considered necessary." Prontosil was administered "until the temperature became normal." After completion of treatment when the clinical improvement was noted, patients did not receive any additional therapies beyond this point in time for Study 1. For Study 2, UV light treatments were administered daily "when considered necessary." Patients did not receive any additional UV light therapy beyond the point in time when clinical improvement was noted, which was identical to Study 1. Sulphanilamide was administered at higher doses "until the temperature of the patient became normal." In the sulphanilamide treatment group, this antibacterial drug was administered at a lower dose for the duration of hospitalization. Because the protocols appeared to be similar, including the prespecified clinical endpoints for both studies, we combined the relevant treatment groups into Table 1: the UV light and Prontosil treatment groups from Study 1 and both treatment groups

from Study 2. The deaths that were observed in the studies were excluded from the efficacy analyses (the deaths by treatment arm are tabulated below).

Table 1. Results of Studies 1 and 2 as Reported in the Articles

	Study 1		Study 2	
	UV light	Prontosil	UV light	Sulphanilamide
N	104	106	135	135
Deaths	6	4	4	5
"failed UV therapy"	n/a	n/a	9	n/a
N evaluable for cessation of spread of lesion	98	102	122	130
Cessation of spread of lesion at 48 hours	**75/98 (76.5%)**	**100/102 (98%)**	**89/122 (73%)**	**129/130 (99.2%)**
Cessation of spread of lesion at 72 hours	86/98 (87.8)	101/102 (99%)	103/122 (84.4%)	130/130 (100%)
Cessation of spread of lesion at 96 hours	91/98 (92.9%)	102/102 (100%)	115/122 (94.3%)	130/130 (100%)
Did not have fever	9	10	10	5
N evaluable for resolution of fever	89	92	112	125
Resolution of fever at 48 hours	**43/89 (48.3%)**	**70/92 (76.1%)**	**53/112 (47.3%)**	**94/125 (75.2%)**
Resolution of fever at 72 hours	55/89 (61.8%)	84/92 (91.3%)	67/112 (59.8%)	113/125 (90.4%)
Resolution of fever at 96 hours	66/89 (74.2%)	86/92 (93.5%)	77/112 (68.8%)	122/125 (97.6%)
N that was not "toxic" at baseline	11	5	6	2
N evaluable for cessation of "toxemia" at 48 hours	87	98	116	128
Cessation of "toxemia" at 48 hours	32/87 (39%)	58/98 (60%)	44/116 (37.9%)	60/128 (46.9%)
Recurrence of erysipelas	12(11.5%)	9 (8.5%)	8 (5.9%)	2 (1.5%)*
Complications	32 (30%)	23 (21%)	28 (20.7%)	11 (8.1%)*
Average duration of therapy	2.6 exposure	(5 grams total)	1.4 exposure	2.5 days (high dose)

*Patients continued to receive sulphanilamide during entire hospitalization, which resulted in numerically lower rates of recurrence and complications for this treatment group.

The prespecified analysis plan was the comparison of the duration of the clinical findings noted in Table 1, and the articles provided the results at day 1 through day 5 of treatment. Although a specific time point was not prespecified as a primary analysis, the articles highlighted the results of the clinical observations at the 48-hour time point, which appeared to have the largest treatment difference. UV light therapy and antibacterial drug treatments were administered for an average of approximately 2 or 3 days. The administration of antibacterial drug therapy was not summarized by the duration of administration in Study 1. Rather, administration of drug therapy was summarized by the average cumulative dose (5 grams total), which can be inferred

to be approximately 2 or 3 days of antibacterial drug therapy. For some of the study patients, the 48- or 72-hour assessment was an *end-of-therapy* assessment because UV light or antibacterial therapy was discontinued during this time frame.

To estimate a treatment effect of an antibacterial drug over *placebo*, we evaluated the results of the cessation of spread of the lesion and resolution of fever after 48 hours, 72 hours, and 96 hours of therapy, as depicted in Tables 2 and 3. The duration of toxemia, which was an estimate of clinical well-being by clinician evaluation of signs and symptoms such as headache, insomnia, vomiting, and prostration, among others, was not fully characterized and the articles noted that "the precise duration of toxaemia [sic] is difficult to assess clinically." Therefore, we did not include *cessation of toxemia* in an estimate of treatment effect, although as shown in Table 1 the proportion of patients with cessation of toxemia at 48 hours in the antibacterial drug treatment groups was numerically higher.

Table 2 summarizes the clinical outcomes and treatment differences at 48-hour, 72-hour, and 96-hour time points among patients with erysipelas assigned to 1 of 2 treatment groups: a sulfonamide antibacterial drug (Prontosil) or UV light therapy.[18]

Table 2. Clinical Assessment at 48-, 72-, and 96-Hour Time Points for Study 1

Treatment	Cessation of spread of erysipelas at 48 hours	Resolution of fever at 48 hours	Cessation of spread of erysipelas at 72 hours	Resolution of fever at 72 hours	Cessation of spread of erysipelas at 96 hours	Resolution of fever at 96 hours
UV light	75/98 (76.5%)	43/89 (48.3%)	86/98 (87.8%)	55/89 (61.8%)	91/98 (92.9%)	66/89 (74.2%)
Prontosil*	100/102 (98.0%)	70/92 (76.1%)	101/102 (99%)	84/92 (91.3%)	102/102 (100%)	86/92 (93.5%)
Treatment difference Prontosil – UV light (95% CI)	**21.5% (11.7%, 31.3%)**	**27.8% (13.1%, 42.4%)**	11.3% (3.5%, 19.0%)	29.5% (16.6%, 41.4%)	7.1% (1.1%, 14.7%)	19.3% (7.9%, 30.6%)

*Prontosil is metabolized in vivo to sulphanilamide.

Table 3 summarizes the clinical outcomes at 48 hours, 72 hours, and 96 hours among patients with erysipelas assigned to 2 treatment groups: a sulfonamide antibacterial drug (sulphanilamide) or UV light therapy.[19]

[18] See reference number 1 in the references section at the end of this guidance.

[19] See reference number 2 in the references section at the end of this guidance.

Table 3. Clinical Assessment at 48-, 72-, and 96-Hour Time Points for Study 2

Treatment	Cessation of spread of erysipelas at 48 hours	Resolution of fever at 48 hours	Cessation of spread of erysipelas at 72 hours	Resolution of fever at 72 hours	Cessation of spread of erysipelas at 96 hours	Resolution of fever at 96 hours
UV light	89/122 (73.0%)	53/112 (47.3%)	101/122 (82.8%)	67/112 (59.8%)	115/122 (94.3%)	77/112 (68.8%)
Sulphanilamide	129/130 (99.2%)	94/125 (75.2%)	130/130 (100%)	113/125 (90.4%)	130/130 (100%)	122/125 (97.6%)
Treatment difference sulphanilamide – UV light (95% CI)	**26.3% (17.5%, 35.1%)**	**27.9% (15.1%, 40.7%)**	17.2% (10.2%, 25.3%)	30.6% (19.2%, 41.2%)	5.7% (0.9%, 11.9%)	28.8% (19.2%, 38.6%)

The greatest treatment effect was noted at the 48-hour time point for both efficacy endpoints. A similar or even greater treatment effect was noted for resolution of fever at 72- and 96-hour time points. Because the 48-hour data for cessation of spread of lesion and resolution of fever represented the greatest treatment effects, we used these data to estimate a treatment effect on the clinical endpoints of cessation of spread of the lesion and resolution of fever. Figures 1 and 2 describe the DerSimonian and Laird random effects meta-analysis of the results of the 2 studies at each clinical endpoint at the 48-hour time point.

Figure 1. Meta-Analysis for Cessation of Spread of Lesion at 48 Hours

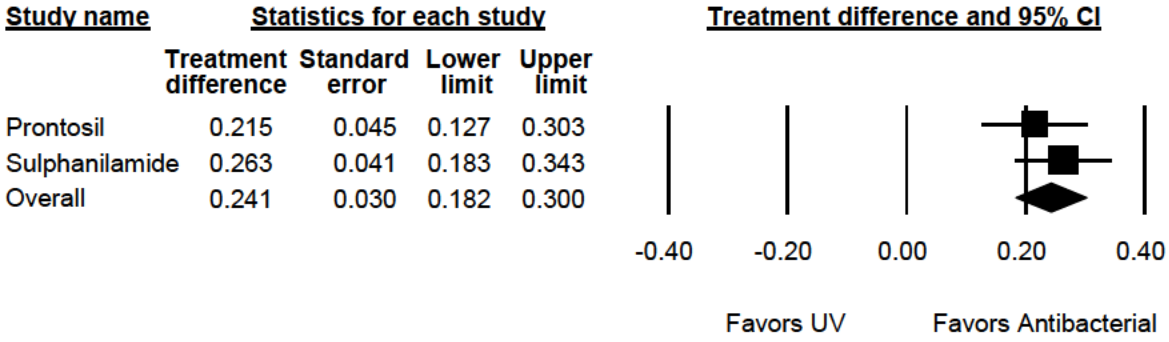
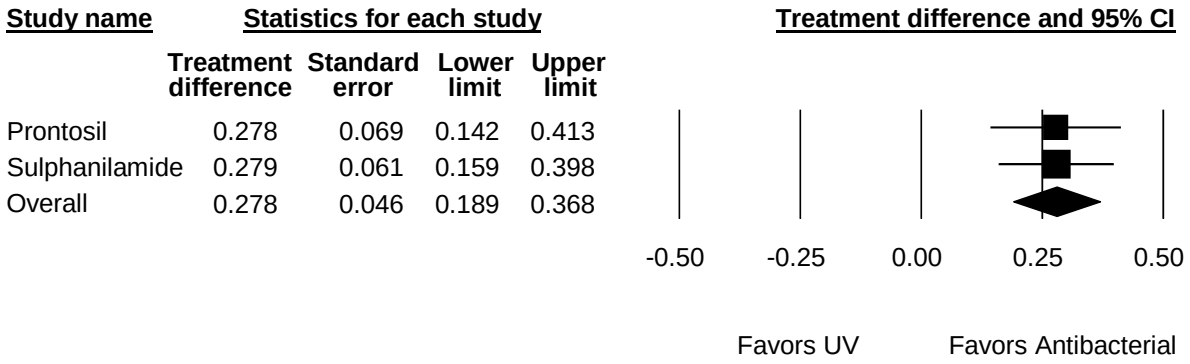


Figure 2. Meta-Analysis for Resolution of Fever at 48 Hours



The results of the two random effects meta-analyses in patients with erysipelas demonstrate that there is a statistically significant treatment difference for the clinical endpoints of cessation of the spread of cellulitis/erysipelas and resolution of fever at 48 hours with the use of sulfonamides compared to UV light. The evaluation of treatment differences in the meta-analyses and the associated lower bound of the 95 percent confidence intervals (CI) accounts for some of the uncertainties and associated variability of the estimate of the treatment differences shown in Figures 1 and 2.

We performed two additional analyses of the data presented in the two articles. Deaths and patients who *failed UV therapy* were excluded from the meta-analyses described in Figures 1 and 2. We included deaths and patients who failed UV therapy as treatment failures (i.e., did not have cessation of spread of the lesion and did not have resolution of fever) in DerSimonian and Laird random effects meta-analyses. We note that the articles do not describe when during the trial these deaths occurred. The treatment differences and 95 percent CI were similar to the results described in Figures 1 and 2. In addition, we used the results as reported in the publications to estimate the proportion of patients that achieved cessation of spread of the lesion *and* resolution of fever as a responder endpoint. We assumed a *worst-case scenario* where we estimated the greatest proportion that might have achieved a successful responder endpoint in the UV light groups and the least proportion in the antibacterial drug groups. For the responder endpoint of cessation of spread of lesion *and* resolution of fever, an estimate of the treatment difference was 26.4 percent with a lower bound of the two-sided 95 percent CI of 17.4 percent. On the basis of these historical data, early objective clinical assessments at 48 to 72 hours after enrollment appear to show the strongest statistically significant differences in the treatment effect of a sulfonamide antibacterial drug over UV light therapy.

The treatment effect of sulfonamides compared to UV light in cellulitis/erysipelas caused by *S. pyogenes* or *S. aureus* for the endpoints of cessation of spread of lesion and the resolution of fever at a 48-hour endpoint was estimated to be approximately 18 percent based on the lower bound of the two-sided 95 percent CI for the two meta-analyses. A conservative estimate of the treatment effect based on a responder endpoint of cessation of spread of lesion and resolution of fever at 48 hours was 17.4 percent (lower bound of the two-sided 95 percent CI). These data show a treatment difference of approximately 17 percent for a responder primary endpoint of cessation of spread of lesion and resolution of fever at a 48- to 72-hour time point. Given the uncertainties and limitations of this data, further discounting is recommended to arrive at an estimate of M1.

Other Pertinent Data From Historical Studies

Several historical studies compared the observed clinical outcomes among patients with cellulitis/erysipelas treated with UV light therapy as the comparator rather than other topical therapies.[20] These studies showed that patients treated with UV light had better outcomes in terms of resolution of local signs and fever. For example, in one study the average time to resolution of symptoms of the infection was 4.5 days for 79 patients treated with UV light and 8.7 days for 151 patients treated with Magnesium sulfate and glycerin pack therapy.[21] Therefore, the treatment effect of antibacterial drug therapy over placebo is likely to be greater than the estimate of the treatment effect based on a UV light control group.

There are historical studies that describe the outcomes of patients with skin infections before the widespread availability of antibacterial drug therapy. One article from Boston City Hospital summarized the outcomes of 122 cumulative cases of *S. aureus* bacteremia. The article did not provide detailed descriptions of the cases, but 12 cases appeared to have skin abscesses as the sole source of bacteremia, with each patient receiving surgical incision and drainage. Only eight patients survived.[22] This article did not provide additional information for the determination of a treatment effect of antibacterial drug therapy over placebo, but demonstrates that morbidity (bacteremia) and mortality was observed in patients with skin abscesses caused by *S. aureus* before availability of antibacterial drug therapies.

Other than the two studies that compared a sulfonamide antibacterial drug to UV light therapy, none of the other studies supported a Historical Evidence of Sensitivity to Drug Effects (HESDE) on a clinical outcome measurement at an early time point after initiation of therapy. Two studies provide some support for early *on-therapy* clinical evaluations for a primary endpoint in noninferiority studies of ABSSSI. For example, skin infections of the hand caused by *S. aureus* or *S. pyogenes* that involved underlying tendon-sheaths showed a mean time to resolution of fever at 3.7 days (standard deviation (SD) ± 2.6 days) for patients that received penicillin therapy and at 12.0 days (SD ± 8.8 days) for patients that did not receive penicillin therapy.[23] Another study evaluated a primary endpoint of "days to no advancement of cellulitis" between patients receiving IV antibacterial drugs in a hospital or at home, and found that approximately 85 percent of all patients in the study had no advancement of cellulitis at a day 2 time point.[24] A recent review examined a number of publications reporting results for patients with skin infections and also supported, in general, the treatment effect of an antibacterial drug in erysipelas and cellulitis.[25]

[20] See reference numbers 3-7 in the references section at the end of this guidance.

[21] See reference number 5 in the references section at the end of this guidance.

[22] See reference number 8 in the references section at the end of this guidance.

[23] See reference number 9 in the references section at the end of this guidance.

[24] See reference number 10 in the references section at the end of this guidance.

[25] See reference number 11 in the references section at the end of this guidance.

The antibacterial drugs used in the Snodgrass papers were sulfonamides.[26] It is reasonable to generalize the effect size of observed for the sulfonamides used in the Snodgrass studies to other antibacterial drugs approved for complicated skin and skin structure infections (or related indications for skin infections) that are also recommended for use in current treatment guidelines. It is reasonable to expect that other antibacterial drug therapies that are both FDA-approved and recommended in treatment guidelines would have at least the effect of a sulfonamide drug in the treatment of ABSSSI. The paper by Spellberg et al. provides some information regarding the observed effect of sulfonamides and penicillin suggesting that the effect of penicillin (during the era when penicillin resistance was not prevalent) was at least as great if not greater than sulfonamides.[27]

A review of other historical studies of cellulitis/erysipelas and skin infections that would be characterized as ABSSSI did not provide additional information of sufficient quality to evaluate the HESDE at an on-therapy endpoint of 48 to 72 hours for a clinical outcome measurement. However, untreated skin infections can be severe, with associated morbidity (bacteremia) and mortality, and early on-therapy clinical evaluations of cessation of spread of cellulitis and resolution of fever as important components of a primary endpoint has some support from historical studies.

Other Studies of Skin and Soft Tissue Infections: Minor Cutaneous Abscess

Placebo-controlled studies that enrolled patients with cutaneous abscesses are available in the literature. Three studies that assessed antibacterial drug therapy versus placebo for the treatment of cutaneous abscesses (incision and drainage was allowed in both treatment groups) did not identify differences in successful outcomes between treatment groups. These studies included patients with varying sizes of the cutaneous abscess and did not characterize the size of the surrounding redness, erythema, and/or induration. In these studies that likely enrolled patients with minor cutaneous abscesses, surgical incision and drainage alone appears to result in high rates of successful outcomes regardless of the presence of systemic antibacterial drug therapy.[28] For example, the determination of clinical cure by resolution of signs and symptoms (e.g., resolution of purulent wound drainage and erythema) at a 1-week *end-of-therapy* assessment did not differ significantly between the treatment groups that received placebo versus an antibacterial drug; 90.5 percent versus 84.1 percent, respectively.[29]

Placebo-controlled studies in patients with varying sizes of cutaneous abscesses that did not characterize the surrounding soft tissue involvement with redness, edema, and/or induration did not demonstrate a treatment effect of antibacterial drugs over placebo in studies where patients received incision and drainage. Minor cutaneous abscesses respond

[26] See reference numbers 1 and 2 in the references section at the end of this guidance.

[27] See reference number 11 in the references section at the end of this guidance.

[28] See reference numbers 12-14 in the references section at the end of this guidance.

[29] See reference number 13 in the references section at the end of this guidance.

to surgical incision and drainage alone. Superiority clinical trials are recommended for clinical trials enrolling patients with minor cutaneous abscesses.

Active-Controlled Clinical Trials

The active-controlled noninferiority trials evaluated clinical responses at a point in time after the completion of therapy, a *test-of-cure* visit, as the primary efficacy endpoint. In general, clinical trials incorporated daily or early clinical assessments, but these results were not routinely reported or systematically examined from the active-controlled trials. Therefore, the active-controlled trials that were used to support approval of antibacterial drugs for treatment of complicated and uncomplicated skin and skin structure infections are not useful for inclusion in a HESDE in the treatment of ABSSSI, based on a noninferiority clinical trial using an efficacy endpoint of 48 to 72 hours after initiation of therapy.

Summary and Selection of Noninferiority Margin for ABSSSI

The overall data support the estimate of M1 to be approximately 12 percent for antibacterial drugs in the treatment of cellulitis/erysipelas for an endpoint of cessation of spread of the lesion *and* resolution of fever at 48 to 72 hours. We believe it is reasonable to generalize this treatment effect to patients with wound infection, major cutaneous abscess, or burn infection where there is a significant component of cellulitis (as defined in section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection) using an endpoint at 48 to 72 hours after clinical trial enrollment. This estimate of M1 has several limitations as described below:

- The HESDE for treatment of ABSSSI was derived only from two studies
- The estimate of M1 was drawn from patients with cellulitis/erysipelas; there were no other studies of patients with other ABSSSI skin infections, such as wound infections, burn infections, or major cutaneous abscesses with surrounding cellulitis that incorporated a placebo or a nonantibacterial drug therapy control group
- The endpoint that was used to estimate a treatment difference of approximately 17 percent was an endpoint at 48 hours of therapy for each clinical observation; the historical studies did not evaluate clinical success as a responder endpoint of both cessation of spread of the lesion and resolution of fever
- The treatment effect was less robust for cessation of spread of the lesion at 72 hours after initiation of therapy
- The treatments were open-label and *randomization* was not clearly described leading to the potential for bias
- Lack of clarity on how the measurements of lesion size were taken in the Snodgrass studies and the associated measurement error

The two studies used to support M1 have the following strengths:

- The investigators prespecified the endpoints of objective daily clinical observations of cessation of spread of lesion and resolution of fever.

- Analyses of the comparison of the duration in time to cessation of spread of lesion and time to resolution of fever were prespecified analyses.

- The treatment differences for resolution of fever were similar between the 48-hour and 72-hour time points.

- Patients received similar background treatment on admission to an "erysipelas ward" in the hospital.

- Maintaining antibacterial drug therapy in Study 2 reduced the proportion of "recurrences" of erysipelas.

- One of the UV light treatment groups may have had fewer patients that were severely ill thereby diminishing an antibacterial drug treatment effect. Twelve "severely ill" patients initially scheduled to receive UV light in Study 2 were removed from the study and received antibacterial drug. None of the 12 patients were expected to survive, but 9 survived and recovered.

- UV light therapy appears to have a better treatment effect compared to other nonantibacterial drug therapies.

- The treatment effect based on the analyses of the two endpoints appears to be similar to the treatment effect based on the analysis of the estimates of a responder endpoint, using conservative estimates of the proportion that achieved a successful responder endpoint of cessation of spread of the lesion *and* resolution of fever at 48 hours.

Given these strengths and limitations, the estimate of the treatment effect over placebo from the lower bound of the 95 percent CI of the treatment difference of approximately 17 percent provide a conservative estimate of the treatment effect. However, this treatment effect should be further discounted to account for the uncertainties listed above. We recommend discounting the treatment effect of 17 percent by approximately 30 percent to account for these uncertainties. Thus, an M1 of approximately 12 percent for the endpoint of cessation of spread of the lesion *and* resolution of fever at 48 to 72 hours appears to be appropriate in the patient population with ABSSSI as defined in section III.A.1, Definitions of Acute Bacterial Skin and Skin Structure Infection. As noted above, if UV light therapy has a treatment effect over placebo, then the true treatment effect of a sulfonamide drug over placebo without UV light may be higher than 17 percent.

These scientific data provide support for an endpoint of cessation of lesion spread and resolution of fever at 48 to 72 hours (i.e., before the completion of drug therapy). From a clinical perspective, clinicians evaluate patients at earlier time points to assess the response to therapy and whether a change in clinical or antimicrobial management is necessary. Patients would be

expected to maintain clinical success during the remainder of administration of investigational drug therapy and after completion of investigational drug therapy; data on clinical outcome at later time points should be captured in the conduct of the clinical trial and reported as secondary efficacy endpoints. Because the clinical evaluations at the end of therapy inform clinicians about a decision to discontinue therapy, and recurrences were noted after a short duration of antibacterial drug therapy (Study 1), we recommend a fixed time point at 10 to 14 days post-randomization as the time of the evaluation of the secondary efficacy endpoint of clinical success or clinical failure.

The clinical studies that were reviewed in general did not offer concise definitions or provide minimum areas of involvement with skin infection. Observational studies of patients presenting with more severe skin infections suggested the potential for morbidity and mortality outcomes in the absence of antibacterial drug therapy. Studies of patients with cutaneous abscesses did not identify a treatment effect of antibacterial drug therapy, perhaps because of the enrollment of patients with smaller or minor cutaneous abscesses that respond readily to incision and drainage alone.

Prontosil or sulphanilamide was used in the clinical studies from which the treatment effect was derived. For future trials it is reasonable to generalize that antibacterial drugs that are FDA-approved for complicated skin and skin structure infections, ABSSSI, or other appropriate-related indications and that are recommended in current treatment guidelines would have at least the effect observed for the sulfonamides used in those clinical studies.

The bacterial pathogens *S. aureus* and *S. pyogenes* were the predominant bacterial pathogens isolated from patients in the historical studies and still represent the most common bacterial pathogens isolated in current studies of ABSSSI. With a sufficiently large area of skin structure or soft tissue involvement with infection that resembles cellulitis/erysipelas, the data that support a noninferiority margin for cellulitis/erysipelas can be extended to wound infections, burn infections, and major cutaneous abscesses. Therefore, precise definitions of skin infections that provide minimum areas of skin involvement are important. A minimum surface area of redness, edema, and/or induration of approximately 75 cm^2 as defined is recommended for ABSSSI as defined in section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection, for the following reasons: (1) it provides a patient population for which the treatment effect of antibacterial drug therapy would be expected to be similar to the treatment effect observed in historical studies of cellulitis/erysipelas; and (2) it provides an extent of disease to clearly and objectively document the infection and to follow clinical improvement or deterioration over time. When the trial is completed, the applicability of the HESDE to the actual population enrolled in the trial should be assessed.

An M1 of 12 percent is estimated for patients with ABSSSI as defined in this guidance using an endpoint of cessation of spread of the lesion and resolution of fever at 48 to 72 hours of therapy. A sufficiently conservative noninferiority margin (M2) should be selected to preserve the treatment effect that antibacterial drugs provide for ABSSSI.

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Appendix 2 US Department of Health and Human Services, US Food and Drug Administration (FDA), Center for Drug Evaluation and Research. *Guidance for Industry: Acute bacterial skin and skin structure infections: Developing drugs for treatment* (October 2013)

Guidance for Industry

Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2013
Clinical/Antimicrobial

Guidance for Industry

Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment

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U.S. Department of Health and Human Services
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TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1]
Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of acute bacterial skin and skin structure infections (ABSSSI).[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for systemic drugs to support an indication for the treatment of ABSSSI. This guidance defines ABSSSI as cellulitis/erysipelas, wound infection, and major cutanenous abscess.

This guidance does not address less serious skin infections, such as impetigo and minor cutaneous abscess,[3] as well as infections needing more complex treatment regimens, such as infections resulting from animal or human bites, necrotizing fasciitis, diabetic foot infection, decubitus ulcer infection, myonecrosis, and ecthyma gangrenosum. Sponsors interested in development of drugs for treatment of skin infections not covered in this guidance should discuss clinical development plans with the FDA.

This guidance also does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*

[1] This guidance has been prepared by the Division of Anti-Infective Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] Sponsors interested in the development of drugs for treatment of impetigo or minor cutaneous abscess should discuss their development plans with the FDA. In general, such trials should be designed for a finding of superiority; see the transcripts of the discussion at the November 18, 2008, Anti-Infective Drugs Advisory Committee (AIDAC) meeting.

Principles for Clinical Trials and *E10 Choice of Control Group and Related Issues in Clinical Trials*.[4]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

This guidance provides information to assist sponsors developing drugs for the treatment of skin infections that are termed *acute bacterial skin and skin structure infections*.[5] ABSSSI include cellulitis/erysipelas, wound infection, and major cutanenous abscess and have a minimum lesion surface area of approximately 75 cm^2. Common bacterial pathogens causing ABSSSI are *Streptococcus pyogenes* and *Staphylococcus aureus* including methicillin-resistant *S. aureus*. Less common causes include other *Streptococcus* species, *Enterococcus faecalis*, or Gram-negative bacteria.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Definitions of Acute Bacterial Skin and Skin Structure Infection

An ABSSSI is defined as a bacterial infection of the skin with a lesion size area of at least 75 cm^2 (lesion size measured by the area of redness, edema, or induration).[6] The minimum area of involvement of 75 cm^2 is chosen to select patients with acute bacterial skin infections for which a reliable control drug treatment effect can be estimated, given that most drugs for ABSSSI will be

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

[5] Public discussions, including the AIDAC meeting on November 18, 2008, discussed the previous characterization of skin and skin structure infections into two broad categories: (1) uncomplicated skin and skin structure infections; and (2) complicated skin and skin structure infections. In addition to suggestions for re-characterizing categories of skin and skin structure infections, noninferiority clinical trial designs and endpoints were discussed. Transcripts and briefing information from the AIDAC meeting can be found at the FDA Web site at http://www fda.gov/ohrms/dockets/ac/cder08.html#AntiInfective.

[6] For areas of ABSSSI that involve certain body surface sites, such as the face, or for young children when it is appropriate to enroll them in a phase 3 clinical trial, sponsors can discuss with the FDA the proposed definitions of ABSSSI that are based on a surface area smaller than 75 cm^2.

studied using noninferiority trial designs.[7] A sufficiently large lesion size also differentiates between *minor cutaneous abscess* (smaller than approximately 75 cm^2) and *major cutaneous abscess* (greater than approximately 75 cm^2). This distinction is important because there appears to be insufficient information to reliably estimate a quantitative treatment effect of an antibacterial drug for patients who have surgical incision and drainage for a minor cutaneous abscess (Duong, Markwell, et al. 2010; Lee, Rios, et al. 2004; Llera and Levy 1985; Rajerdran, Young, et al. 2007).

Patients with the following infection types can be enrolled in ABSSSI clinical trials:

- **Cellulitis/erysipelas:** A diffuse skin infection characterized by spreading areas of redness, edema, and/or induration

- **Wound infection:** An infection characterized by purulent drainage from a wound with surrounding redness, edema, and/or induration

- **Major cutaneous abscess:** An infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration

The method of measuring lesion size should be the same across all trial sites. Methods to assess lesion size include, but are not limited to, the following: (1) manual measurement of length multiplied by perpendicular width; (2) digital planimetry; and (3) computer-assisted tracings.

2. Efficacy Considerations

Noninferiority trials are interpretable and acceptable to support approval of a drug for an indication of the treatment of ABSSSI. A showing of superiority to an effective control is also readily interpretable and would be acceptable.

If an indication for the treatment of ABSSSI is the sole indication for which the drug has been, or is being, developed, then two adequate and well-controlled trials generally are recommended to provide evidence of effectiveness. A single adequate and well-controlled trial supported by other independent evidence, such as a trial in another infectious disease indication (e.g., treatment of community-acquired bacterial pneumonia), could also provide evidence of effectiveness in the treatment of ABSSSI.[8] Sponsors should discuss with the FDA other independent confirmation that would be used to support the findings from a single trial in ABSSSI.

3. Safety Considerations

In general, we recommend a preapproval safety database of approximately 700 patients or more. If the same or greater dose and duration of therapy for the treatment of ABSSSI were used in

[7] See the Appendix and the draft guidance for industry *Non-Inferiority Clinical Trials* (when final, this guidance will represent the FDA's current thinking on this topic).

[8] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

clinical trials for other infectious disease indications, the safety information from those clinical trials can be part of the overall preapproval safety database. For new drugs that have an important clinical benefit compared to existing therapies, depending on the benefit demonstrated, a smaller preapproval safety database may be appropriate. Sponsors should discuss the appropriate size of the preapproval safety database with the FDA during clinical development.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Designs, Populations, and Entry Criteria

The clinical trial population for efficacy trials should include male and female patients with a mixture of the ABSSSI disease entities (e.g., cellulitis/erysipelas, wound infection, major cutaneous abscess) described in section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection. Because surgical incision and drainage might influence treatment outcomes among patients with major cutaneous abscesses, patients with major cutaneous abscesses should not comprise more than 30 percent of the clinical trial population.

2. General Exclusion Criteria

Recommended general exclusion criteria include the following:

- Patients with medical conditions that would alter the interpretation of a primary endpoint (e.g., patients with neutropenia)
- Patients with suspected or confirmed osteomyelitis
- Patients with suspected or confirmed septic arthritis
- Patients who have received more than 24 hours of effective antibacterial drug therapy for treatment of the current episode of ABSSSI (see section III.B.4., Prior Antibacterial Drug Therapy)

3. Clinical Microbiology Considerations

Sponsors should obtain an adequate clinical specimen for microbiologic evaluation (e.g., pus from a wound or abscess; an aspirate from the leading edge of cellulitis), including culture, Gram stain, and in vitro antibacterial susceptibility testing performed on appropriate organisms isolated from the specimen. Specimens should be processed according to recognized methods (e.g., American Society for Microbiology 2011). The specimen for microscopic evaluation and culture, as well as blood cultures from two separate venipuncture sites, should be obtained before administration of antibacterial therapy, if possible. This microbiological information is important for characterizing the underlying bacterial etiologies of ABSSSI.

Sponsors should save all isolates considered possible pathogens taken from patients enrolled in clinical trials in the event that additional testing of an isolate is needed (e.g., pulse field gel electrophoresis for strain identification).

Rapid diagnostic tests can be used for enrichment of trial populations with specific infections. In addition, the clinical trial of an antibacterial drug may provide an opportunity to contribute to the development and evaluation of a new diagnostic test. Sponsors interested in the development of a new diagnostic test should discuss potential approaches with the FDA.

4. Prior Antibacterial Drug Therapy

Ideally, patients enrolled in an ABSSSI clinical trial would not have received prior antibacterial drug therapy because such therapy can have a number of potential consequences for a clinical trial. Prior antibacterial drug therapy could:

- Obscure any potential treatment differences between an investigational drug and control drug and therefore bias toward a finding of no difference (i.e., a bias toward noninferiority)

- Influence the evaluation of efficacy findings based on an endpoint earlier in therapy (48 to 72 hours)

However, a complete ban on prior antibacterial therapy could have adverse consequences, including:

- Exclusion of all patients who received prompt administration of antibacterial drug therapy because of the severity of their disease could result in a patient population with lesser severity of illness and greater potential for spontaneous recovery; trial results could therefore be biased toward a finding of no difference between treatment groups (i.e., a bias toward noninferiority)

- Certain trial sites may not participate in the clinical trial because of concerns regarding standard-of-care treatment.

A pragmatic approach to these concerns is to: (1) encourage prompt enrollment procedures so that patients can receive the clinical trial treatment initially, with no need for other antibacterial drug therapy; and (2) allow enrollment of some patients who have received a single dose of a short-acting antibacterial drug within 24 hours of enrollment (e.g., ideally there would be few such patients, and they could be limited to 25 percent of the patient population). This would allow patients in the trial to receive prompt antibacterial drug therapy if that was clinically necessary, consistent with the standard of care. The results in the subgroup of patients (i.e., the majority of patients) who did not receive prior effective antibacterial drug therapy will be important to evaluate and the primary analysis can be stratified by prior therapy to assess the consistency of the results across the two subgroups (i.e., patients who received prior therapy and those who did not receive prior therapy).

There are other circumstances in which patients who received prior antibacterial drug therapy can be eligible for clinical trial entry:

- Objective documentation of clinical progression of ABSSSI while on antibacterial drug therapy (i.e., not by patient history alone)

- The patient received an antibacterial drug for surgical prophylaxis and subsequently develops ABSSSI

5. Concurrent Antibacterial Drug Therapy

Ideally, concurrent antibacterial drug therapy should be avoided. However, certain patients with ABSSSI could receive additional empirical antibacterial drug treatment, preferably treatment that has no overlapping antibacterial activity with the investigational drug. For example, a patient who has a new diagnosis of ABSSSI while in the hospital (e.g., wound infection) might require empirical antibacterial drug therapy that treats both Gram-positive and Gram-negative bacterial pathogens; such a patient could enroll in a trial for an investigational drug that has only Gram-positive antibacterial activity, provided that the concurrent empirical antibacterial drug for Gram-negative treatment does not have overlapping Gram-positive antibacterial activity with the investigational drug.

6. Adjunctive Therapy

The following adjunctive therapy is often used in ABSSSI treatment:

- Daily dressing changes

- Use of topical solutions including nonspecific antimicrobial drugs such as povidone-iodine

- Debridement

- Hyperbaric oxygen treatments

- Surgical interventions planned at the initiation of treatment

Sponsors should specify which adjunctive therapies are to be permitted in the clinical trials. With proper blinding and randomization, both the investigational drug group and control group should have comparable use of these adjunctive therapies. Sponsors should analyze the clinical outcomes stratified by the presence or absence of adjunctive therapies (e.g., daily debridement). Topical treatments with specific antibacterial activity should not be used as adjunctive therapy in ABSSSI clinical trials.

7. Efficacy Endpoints and Timing of Assessments

a. Primary efficacy endpoint of lesion response at 48 to 72 hours

Clinical response should be based on the percent reduction in the lesion size at 48 to 72 hours compared to baseline, measured in patients who did not receive rescue therapy and are alive. A

clinical response in a patient generally is defined as a percent reduction in lesion size greater than or equal to 20 percent compared to baseline.[9] Alternative metrics of lesion response should be discussed with the FDA before initiation of clinical trials.

b. Secondary endpoint considerations

Resolution of ABSSSI evaluated at 7 to 14 days after completion of therapy should be a secondary endpoint.

Refinement of the clinical outcome assessments in ABSSSI trials (e.g., lesion size measurements other than length times width) can be considered.[10] In addition, symptoms, including pain, caused by ABSSSI can be important to evaluate.[11]

8. Trial Procedures and Timing of Assessments

a. Entry visit

At this visit, sponsors should collect appropriate demographic information, history and physical examination findings, lesion size measurements, microbiological specimens, and safety laboratory tests.

b. On-therapy visit at approximately 48 to 72 hours

At this visit, sponsors should evaluate the lesion size in the same manner as at the entry visit, as specified by the protocol. Safety and laboratory tests, as appropriate, should be evaluated.

c. End-of-therapy visit

At this visit, sponsors should evaluate the lesion size in the same manner as at the entry visit, as specified by the protocol. Safety and laboratory tests, as appropriate, should be evaluated. Assessment of whether discontinuation of antibacterial drug therapy is appropriate also can be made.

d. After-therapy visit

This visit should correspond to a visit within a window of approximately 7 to 14 days after the last day of therapy. Sponsors should assess the maintenance of clinical response and any new safety effects or safety laboratory tests, as appropriate, at this visit. A day-28 all-cause mortality assessment is recommended.

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[9] See, for example, Talbot, Powers, et al. 2012.

[10] See Talbot, Powers, et al. 2012.

[11] For more information, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

9. Statistical Considerations

In general, sponsors should provide a detailed statistical analysis plan stating the trial hypotheses and the analysis methods before trial initiation. The primary efficacy analysis is based on the difference in the proportions of patients achieving a successful clinical response (e.g., at least a 20 percent reduction in the lesion size at 48 to 72 hours when compared to baseline). An exploratory analysis that compares clinical responses among patients who received prior antibacterial drug therapy and patients who did not receive prior antibacterial drug therapy should be considered.

a. Analysis populations

The definitions for the statistical analysis populations are provided as follows:

- Safety population — All patients who received at least one dose of drug during the trial.
- Intent-to-treat (ITT) population — All patients who were randomized.
- Microbiological intent-to-treat (micro-ITT) population — All patients randomized to treatment who have a baseline bacterial pathogen known to cause ABSSSI. Patients should not be excluded from this population based upon events that occur after randomization (e.g., lost to follow-up).
- Per-protocol, clinically evaluable, or microbiologically evaluable populations — Patients who follow important components of the trial can then be defined as part of a per-protocol or other evaluable population (i.e., ITT patients who follow important components of the trial can be defined as the clinically evaluable population, or micro-ITT patients who follow important components of the trial can be defined as the microbiologically evaluable population).

In general, sponsors should consider the ITT population to be the primary analysis population because the definitions of ABSSSI described in section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection, are most consistent with bacterial infectious diseases even for cases in which purulent material is not easily obtained (e.g., cellulitis). For an antibacterial drug with targeted activity against a specific pathogen or class (e.g., a drug with antibacterial activity against Gram-negative pathogens), sponsors should discuss the appropriate analysis population with the FDA. Generally, it is not appropriate, as a scientific matter, to consider analyses of the per-protocol population as primary, because population membership is based on after randomization events or characteristics of patients. However, consistency of the results should be evaluated in all populations.

b. Noninferiority margins

A noninferiority margin of 10 percent for the primary efficacy endpoint based on a reduction in lesion size at 48 to72 hours (defined in section III.B.7., Efficacy Endpoints and Timing of

Assessments) is supported by the historical evidence (see the Appendix).[12] Sponsors should discuss the selection of a noninferiority margin with the FDA in advance of trial initiation, particularly for a proposed margin of greater than 10 percent or for a margin using an endpoint other than lesion response based on the reduction in lesion size (i.e., the proportion of patients achieving at least a 20 percent reduction in lesion size).

c. Sample size

An estimate of the sample size for a noninferiority trial with 1:1 randomization is approximately 310 patients per arm based on the following assumptions: (1) the noninferiority margin is selected at 10 percent; (2) the type I error is 0.05; (3) the type II error is 0.10 (90 percent power); and (4) 80 percent of patients achieve clinical success with the comparator drug.

10. Specific Populations

Sponsors should discuss drug development in the pediatric populations as early as is feasible. The Pediatric Research Equity Act (PREA), as amended by the Food and Drug Administration Safety and Innovation Act, states that initial plans for the conduct of pediatric studies (referred to as an *initial pediatric study plan*) shall be submitted to the FDA before the date on which required pediatric assessments are submitted under PREA and no later than: (1) 60 days after the end-of-phase 2 meeting; or (2) such other time as may be agreed upon by the Secretary and the applicant.[13] In most situations, the course of the disease and the effects of therapy for ABSSSI are sufficiently similar in the adult and pediatric populations. Accordingly, under those circumstances, adult efficacy findings for drugs to treat ABSSSI may be extrapolated to the pediatric population. Pharmacokinetic (PK) and safety studies should be conducted to determine dosing in the pediatric population that provides exposure similar to exposure that is effective in adults and safety information at the identified dose(s). Drug development programs should include a sufficient number of geriatric patients (e.g., older than 65 years of age and older than 75 years of age) to characterize safety and efficacy in this population.[14]

C. Other Considerations

1. Pharmacokinetic/Pharmacodynamic Considerations

Sponsors should evaluate the PK/pharmacodynamic (PD) characteristics of the drug using in vitro models or animal models of infection. The results from nonclinical PK/PD assessments should be integrated with the findings from phase 1 PK assessments to help identify appropriate

[12] See the draft guidance for industry *Non-Inferiority Clinical Trials*.

[13] See PREA (Public Law 108-155; section 505B of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. 355c) as amended by the Food and Drug Administration Safety and Innovation Act of 2012 (Public Law 112-114) and the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

[14] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers*.

dose and dosing regimens for evaluation in phase 2 and phase 3 clinical trials. Plasma drug concentrations should be determined from patients in phase 2 clinical trials. Using the plasma concentration data, the sponsor should assess the relationship between antibacterial PK/PD indices and observed clinical and microbiological outcomes. Antibacterial PK/PD indices include maximal unbound drug concentration [fCmax]/minimum inhibitory concentration (MIC) ratio, area under the unbound drug concentration-time curve [fAUC]/MIC ratio, or the percentage of the dosage interval that the unbound drug concentration exceeds the MIC [fT>MIC]. The evaluation of exposure-response relationships (efficacy and safety) in phase 2 helps determine the best dose for evaluation in phase 3 trials. PK samples can be obtained by various approaches, such as rich or sparse sampling obtained from specific subsets of patients and/or at specific trial sites.

Sponsors may want to consider obtaining plasma drug concentrations from patients in phase 3 clinical trials. The concentration data are most important when the population studied in phase 3 differs from the population studied in phase 2 (e.g., the phase 3 population has more severe illness). If phase 3 trials include a previously unstudied specific population, such as patients with renal or hepatic impairment, collection of plasma drug concentrations from those specific populations can aid in determining necessary dose adjustments. The concentration data can also help with the interpretation of any unexpected safety or efficacy findings.

2. Dose Selection and Formulation

Sponsors should integrate the findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics, pharmacodynamics, in vitro susceptibility profiles of target pathogens, safety and tolerability information from phase 1 trials, and safety and antibacterial activity information from phase 2 dose-ranging trials for purposes of selection of appropriate doses, dosing regimens, and duration of therapy to be evaluated in phase 3 clinical trials.

For drugs that only have an intravenous (IV) formulation available, we recommend that patients receive the IV formulation alone until the assessment of the primary efficacy endpoint (e.g., at 48 to 72 hours), without a switch to an FDA-approved oral antibacterial drug, if feasible.

For drugs that have both an IV and oral formulation, a switch to the oral drug may be appropriate before the primary efficacy outcome assessment at 48 to 72 hours provided that pharmacokinetics of the oral formulation have been evaluated to ensure adequate exposure and to determine an appropriate dosing regimen.

3. Labeling Considerations

The labeled indication for a drug approved for the treatment of ABSSSI should be for the treatment of ABSSSI caused by specific bacteria identified in patients in the clinical trials. For example:

> *"Drug X is indicated for the treatment of acute bacterial skin and skin structure infections due to … [list genus and species of bacteria]."*

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APPENDIX: JUSTIFICATION FOR A NONINFERIORITY MARGIN FOR ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

Background

The first step in the consideration for a noninferiority trial design is determining the treatment effect of the active-comparator drug that can be reliably distinguished from placebo (M_1). This margin is based on evidence from previously conducted trials using reliable efficacy endpoints.[15] For ABSSSI, there were no placebo-controlled trials reported in the historical literature. However, two controlled trials evaluated antibacterial drugs versus nonantibacterial treatments in patients with cellulitis/erysipelas. These two studies can be used to estimate the treatment difference for antibacterial drugs in the treatment of ABSSSI for the endpoint based on lesion size assessment.

Controlled Studies in Cellulitis/Erysipelas

Two controlled studies were identified in the scientific literature that compared outcomes in patients with cellulitis/erysipelas treated with an antibacterial drug versus ultraviolet (UV) light therapy (Snodgrass and Anderson 1937(a); Snodgrass and Anderson 1937(b)). During the 1930s, UV light was routinely used because previous studies published in the mid-1930s showed potential benefit in erysipelas when compared to other nonantibacterial therapies. UV light therapy was the control group in these studies.

Both studies enrolled patients with clinically documented erysipelas; however, the identification of a bacterial pathogen was not reported among study patients. Erysipelas and cellulitis can be difficult to distinguish clinically and physicians use both terms to describe skin infections of the upper dermis or subcutaneous tissues. We inferred that these two studies enrolled patients with cellulitis/erysipelas (ABSSSI) caused by either *S. pyogenes* or *S. aureus*.

In the first study (Snodgrass and Anderson 1937(a)), 312 patients admitted from May 1936 to February 1937 received one of four open-label treatments for erysipelas:

- UV light
- Prontosil (a sulfonamide antibacterial drug that is metabolized to sulphanilamide)
- UV light plus Prontosil
- Scarlet fever antitoxin

In the second study (Snodgrass and Anderson 1937(b)), 270 patients admitted from February 1937 to August 1937 received one of two open-label treatments for erysipelas:

- UV light
- Sulphanilamide (a sulfonamide antibacterial drug)

[15] See the draft guidance for industry *Non-Inferiority Clinical Trials*.

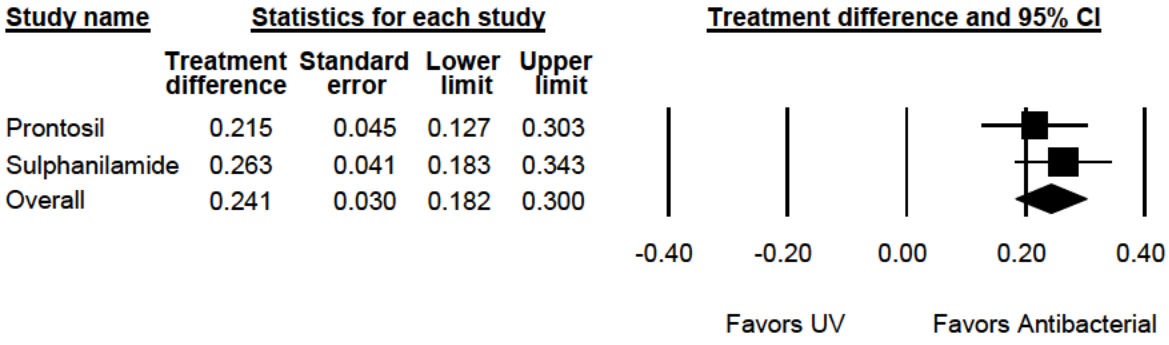
The efficacy endpoints were prespecified as clinical observations of whether the *lesion continues to spread*, the *temperature has become normal*, and the patient *continues in a toxic condition*. The largest treatment difference in lesion spread was the evaluation at 2 days; a smaller treatment difference was noted at day 3 and there was no difference in cessation of lesion spread at the day 4 time point. Because the authors described cessation of lesion spread at *day 0*, then at *day 1*, followed by *day 2*, and so forth, we assumed that the evaluation at day 2 represented an evaluation at approximately 48 to 72 hours of therapy (i.e., day 0 represented the assessment of the patients' lesions after some amount of time on therapy during the first day of hospitalization).

To estimate a treatment effect of an antibacterial drug, we evaluated the results of the cessation of spread of the lesion after 2 days of therapy. Table A provides summary information about the results of cessation of the spread of the lesion. Figure A shows the results of a random effects meta-analysis.

Table A. Results of Studies 1 and 2 as Reported in the Articles

	Study (a)		**Study (b)**	
	UV light	Prontosil	UV light	Sulphanilamide
N	104	106	135	135
Deaths	6	4	4	5
Treatment discontinuations	0	0	9	0
N evaluable for cessation of spread of lesion	98	102	122	130
Cessation of spread of lesion at 2 days (i.e., 48-72 hours)	**75/98 (76.5%)**	**100/102 (98%)**	**89/122 (73%)**	**129/130 (99.2%)**

Figure A. Meta-Analysis for Cessation of Spread of Lesion at 2 Days



The results of the random effects meta-analysis in patients with erysipelas demonstrate that there is a statistically significant treatment difference for the endpoint of cessation of the spread of cellulitis/erysipelas in favor of sulfonamides compared to UV light. The treatment effect of sulfonamides compared to UV light in cellulitis/erysipelas was estimated to be approximately 24 percent with a lower 95 percent confidence bound of approximately 18 percent based on the meta-analysis of the two studies.

An early on-therapy clinical evaluation as a primary efficacy endpoint in ABSSSI has support from other publications:

- Skin infections of the hand caused by *S. aureus* or *S. pyogenes* that involved underlying tendon-sheaths showed a mean time to resolution of fever at 3.7 days for patients that received penicillin and at 12.0 days for patients that did not receive an antibacterial drug (Florey and Williams 1944)

- A primary endpoint of *days to no advancement of cellulitis* found that approximately 85 percent of all patients in the trial had no advancement of cellulitis at a day 2 time point regardless of whether the patient received the antibacterial drug therapy in a hospital or at home (Corwin, Toop, et al. 2005)

- Before the availability of antibacterial drugs in 1928, 142 patients with erysipelas were treated with nonantibacterial therapies (intramuscular administration of horse serum antitoxin) and 78.1 percent were considered *cured* at day 7 (Symmers 1928), suggesting that an efficacy evaluation for antibacterial drugs much earlier than day 7 is appropriate for the noninferiority trial design in ABSSSI

The treatment difference estimated from the two studies cited above is probably a conservative estimate for the following reasons:

- UV light therapy appeared to result in more favorable outcomes among patients with cellulitis/erysipelas (Lavender and Goldman 1935; Titus 1934; Ude and Platou 1930; Ude 1931; Sutherland and Day 1935)

- Before the availability of antibacterial drug therapy, morbidity (bacteremia) and mortality were observed in patients with skin abscesses caused by *S. aureus* (Skinner and Keefer 1941)

- In comparison to a sulfonamide antibacterial drug, antibacterial drugs available today are probably more effective therapies for ABSSSI (Spellberg, Talbot, et al. 2009)

Summary and Selection of Noninferiority Margin for ABSSSI

The overall data support the treatment difference to be conservatively estimated at 18 percent for antibacterial drugs in the treatment of ABSSSI for the endpoint based on lesion size assessment. Because this appears to be a conservative estimate, further discounting of the treatment effect may not be necessary and thus M_1 is estimated to be 18 percent. These scientific data provide support for the selection of a noninferiority margin of 10 percent that preserves some of M_1 based on an endpoint of lesion size assessment. Sponsors should discuss the selection of a noninferiority margin greater than 10 percent with the FDA in advance of trial initiation.